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## Research Submission

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# The Neuropsychology of Cluster Headache: Cognition, Mood, Disability, and Quality of Life of Patients With Chronic and Episodic Cluster Headache

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**Background.**—Cluster headache (CH) is commonly regarded as one of the most disabling headache conditions, and referred to as one of the most painful conditions known to humankind. Although there has been some research indicating the severe impact of CH, there is little comprehensive evidence of its impact on quality of life, disability, mood, and cognitive function in both its episodic (ECH) and chronic (CCH) variants.

**Methods.**—This cross-sectional study investigates various aspects of cognitive function including intelligence, executive function, and memory, and mood, disability, and quality of life in 22 patients with ECH and CCH compared with age-matched healthy controls.

**Results.**—The results showed that intelligence and executive functions are intact in patients with CH, but that patients with CH perform significantly worse than healthy controls on tests of working memory and (all  $P < .05$ ) report greater cognitive failures ( $P < .05$ ). Around one third of both the ECH and CCH groups achieved “caseness” for depression, while self-reported anxiety was higher in those with CCH than the ECH patients, with 75% of the former compared with 38% of the latter groups achieving “caseness” on the measure of anxiety. Patients with CH reported high levels of disability, which was not significantly different between the 2 groups ( $P > .05$ ). The patients with CH reported poor quality of life compared with healthy controls; however, this difference was not statistically significant.

**Conclusion.**—Patients with CH show worse working memory, disturbance of mood, and poorer quality of life compared with healthy controls. The differences between patients with ECH and CCH, and the implications of these findings for the management of CH are discussed.

**Key words:** chronic cluster headache, episodic cluster headache, cognition, mood, disability, quality of life

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**Abbreviations:** BDI Beck Depression Inventory; BHS Beck Hopelessness Scale, CCH chronic cluster headache, CFQ Cognitive Failures Questionnaire, CH cluster headache, CVLT California Verbal Learning Test, D-KEFS Delis–Kaplan Executive Function System, ECH episodic cluster headache, EQ5D EuroQoL, FSIQ Full Scale Intelligence Quotient, HADS-A Hospital Anxiety Depression Rating Scale-Anxiety, HADS-D Hospital Anxiety and Depression Rating Scale, HCs healthy controls, HIT Headache Impact Test, IQ intelligence quotient, MANOVA multivariate analysis of variance, MIDAS Migraine Disability Assessment Scale, MMSE Mini-Mental State Examination, NART National Adult Reading Test, QoL quality of life, SCOPA-AUT Scales for Outcomes in Parkinson's disease – Autonomic, SRMF Short Recognition Memory for Faces, TMT Trial Making Test, VF verbal fluency, WAIS Wechsler Adult Intelligence Scale, WASI Wechsler Abbreviated Scale of Intelligence, WMI Working Memory Index

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Cluster headache (CH) is considered to be one of the most painful conditions known to humankind, with female patients describing the headache attacks as being more painful than childbirth.<sup>1,2</sup> There are 2 types of CH, episodic (ECH) and chronic (CCH), and while the pain experienced by both groups is similar, they are distinguished by the frequency of the attacks.<sup>3</sup> CH usually occurs in cluster periods and is therefore more commonly ECH, while only around 15-20% of the patients suffer from CCH without remission.<sup>3</sup>

Patients suffering from CH experience unilateral pain and due to the excruciating intensity of the pain, violent self-harm at the site of the pain and attempted suicide are often reported.<sup>4,5</sup> Inevitably, this painful condition has a negative influence on the patient's life and general well-being.

There has been some research looking at the impact of CH on quality of life (QoL) and daily functioning. These have shown poorer well-being on many domains of QoL<sup>6,7</sup> and increased disability due to the impact of the headache.<sup>8-10</sup> The level of impairment in QoL in CH has been reported to be similar to that documented in migraine,<sup>7</sup> while disability due to headache has been reported to be higher in patients with CH than those with migraine.<sup>8</sup> However, while migraine is very well researched and there is much evidence illustrating its impact, the influence of CH continues to be under-represented. Similarly, there is limited evidence documenting the psychological well-being of patients with CH. Researchers have shown that patients with CH experience high levels of

anxiety disorders<sup>9,11</sup> and increased depression, agoraphobic symptoms, and suicidal tendencies relative to healthy controls (HCs).<sup>8</sup> A recent population-based follow-up study also showed that patients with CH are at a greater risk of developing depression compared with HCs.<sup>12</sup>

In addition to the adverse impact that CH has on the patient's life and general well-being, cognitive dysfunction has also been associated with CH. Since the structures known to serve memory and executive function are involved in the development of CH,<sup>13-17</sup> there has been some investigation of cognitive function in CH. While some researchers have shown impairments in verbal memory functions,<sup>11</sup> others report no significant differences in memory or executive function between participants with CH and HCs.<sup>18</sup> Similarly, data obtained from neurophysiological studies suggest that cognitive processing in CH is affected only during active headache attacks and therefore propose that any impairment may be due to the pain experienced.<sup>19-21</sup> According to studies looking at the impact of pain on cognitive performance, chronic and persistent pain stimuli can be highly demanding of attentional resources which can then impair cognitive performance.<sup>22,23</sup>

These studies highlight the marked negative influence that CH can have on the patients' lives, compromising their sense of well-being and their ability to function normally. However, the majority of these studies are based on either patients with ECH or CCH alone, or they lack appropriate comparison of the data to a normal population to illustrate the

clinical significance of any differences found.<sup>7,10,11,18</sup> Thus in an attempt to provide a clearer account of the impact that both ECH and CCH can have on the patients lives, we aim to investigate key components of cognitive (intelligence, executive function, and memory) and psychosocial function (mood, disability, and QoL) compared with a matched HC group.

## METHODS

**Sample.**—The sample consisted of 3 groups: CCH (N = 11), ECH (N = 11), and HCs (N = 12) (please see Table 1 for details). The patients with CH were consecutively recruited from the outpatient clinic of the tertiary headache referral center at the National Hospital for Neurology and Neurosurgery (Queen Square, London). The sample size was derived from the number of cases attending the tertiary clinic that met the inclusion criteria. This size was considered adequate based on previous studies investigating this subject in this client group.

The patients with CH fulfilled the International Headache Classification (ICHD-II) criteria for ECH and CCH.<sup>3</sup> According to this classification, CCH consists of 10-15 continuous attacks without remission that last between 15 and 180 minutes and occur between 1 and 8 times per day. ECH consists of 2 cluster attacks for at least 7 days that can last for several weeks or months, and are separated by a remission period of several months to many years. For

better comparison of performance, ECH patients in this sample were tested during an active headache bout. Patients with other co-existent headache disorders and/or history of any psychiatric or neurological condition, head injury, or those that had received surgical treatment for CH were excluded.

The HCs were the spouses of the patients seen at the clinic, who also had no history of headache diagnoses, psychiatric illness, head injury, or any neurological illness.

**Procedure.**—This study was approved by the Local Ethics Committee and conforms to the Declaration of Helsinki guidelines. All participants gave written informed consent.

All participants were assessed using validated instruments for measuring cognitive and psychosocial functioning for the purposes of this study only.

The data for this study were collected during 2011 and 2012.

**Cognitive Assessment.**—The participant's global cognitive functioning, intelligence, executive functioning, and memory were measured using the following assessment tools:

*Global Cognitive Functioning and Intelligence.*—Mini-Mental State Examination (MMSE)<sup>24</sup> is a 30-item measure of global cognitive functioning covering: orientation, memory, language, and executive function. The score range is 0-30, with higher scores representing better cognitive functioning. Scores

**Table 1.—Demographic and Clinical Details of Patients with Episodic (ECH) or Chronic Cluster Headache (CCH) and Healthy Controls (HCs)**

	HC (n = 12)	ECH (n = 11)	CCH (n = 11)	P
Age (years)	53.17 ± 16.25	40.82 ± 15.11	49.18 ± 11.02	.552
Gender				
Male	33%	73%	82%	.038
Female	67%	27%	18%	
Education (years)	14.50 ± 2.15	15.27 ± 2.76	14.36 ± 4.20	.642
Age at onset (years)		30.00 ± 17.60	34.55 ± 10.85	.341
Disease duration (years)		10.82 ± 15.15	14.64 ± 11.48	.232
CH side				
Left (%)		18%	45.5%	.264
Right (%)		73%	45.5%	
Bilateral (%)		9%	0%	
Unilateral (%)		0%	9%	

below 24 are considered to indicate cognitive impairment.

The National Adult Reading Test (NART)<sup>25</sup> is a test of premorbid intelligence quotient (IQ) that requires participants to read out loud a set of 50 English words that are presented in order of increasing difficulty. The test taps vocabulary and reading ability, 2 areas of cognitive function least affected by cognitive decline, and thus commonly used to estimate premorbid IQ. The words presented have irregular grapheme and phoneme correspondence, and thus accurate reading would require previous knowledge of the word. The total error score is used to estimate premorbid IQ.

The Wechsler Abbreviated Scale of Intelligence (WASI)<sup>26</sup> is a measure of current IQ, consisting of 4 subscales: vocabulary, similarities, block design, and matrix reasoning. In the abbreviated version, the vocabulary and matrix reasoning subtests are used to calculate the full-scale IQ. The vocabulary subtest measures the individual's verbal knowledge and verbal concept formation. The matrix reasoning subtest provides information about the patient's non-verbal fluid reasoning such as visual information processing and abstract reasoning skills.

*Executive Functioning.*—The Delis–Kaplan Executive Function System (D-KEFS)<sup>27</sup> is a neuropsychological test of verbal and nonverbal executive functions. It consists of various subtests. In this study, the following subtests were used to assess executive function:

The Trail Making Test (TMT) is a test of behavioral regulation that consists of 5 subtests: (1) visual scanning: the participants crosses out all “3” among both letters and other numbers; (2) number sequencing: the participant connects all numbers in successive order, ignoring any letters on the sheet; (3) letter sequencing: the participant connects letters in alphabetical order, ignoring any numbers on the sheet; (4) number-letter switching: the participant connects circles switching between the ones containing digits and letters (1-A-2-B-. . .) in 2 alternating sequences; and (5) motor speed: measures general motor speed and requires the subject to trace dashed lines connecting empty circles as fast as possible. In addition to scaled scores for each subtest, a contrast score of

“letter-number switching-letter sequencing” score can be computed, directly quantifying relative performance on a baseline task and a higher-level task requiring switching and set shifting.

Verbal fluency (VF) is made up of 3 tasks each performed as fast as possible for 60 seconds: (1) letter fluency: the participant generates words beginning with a particular letter: F, A, S; (2) category fluency: the participant generates words belonging to a designated category: animals, boys' names; and (3) category switching: the participant alternates between generating words from 2 semantic categories, fruit and furniture. For each subtest, the total number of correct words generated is recorded and scaled scores are calculated.

The Color-Word Interference Test (Stroop) assesses the ability to inhibit proponent responses and contains 4 subtests: (1) color naming: naming colored rectangles; (2) word reading: reading the color words red, green, and blue printed in black ink; (3) inhibition: naming the color of ink of color words written in an incongruent ink color (eg, word red printed in green ink); and (4) inhibition/switching: naming the color of ink of color words printed in an incongruent ink and switching to reading the word when the stimulus is presented in a box. Total completion time and self-corrected and uncorrected errors are noted. Scaled scores are obtained for each subtest. An inhibition–color naming contrast score is also computed.

*Verbal and Non-Verbal Memory.*—California Verbal Learning Test (CVLT)<sup>28</sup> is a measure of verbal short-term and long-term memory. It assesses recall and learning across 5 repetitions and recognition of a list of 16 words belonging to 4 semantic categories presented at immediate and delayed recall trials. Immediate presentation and recall of a second list to test proactive interference is followed by testing of free and cued recall of the first trial. Delayed recall is also tested after a 20-minute delay, followed by delayed free and forced choice recognition trials.

The Warrington Short Recognition Memory for Faces (SRMF)<sup>29</sup> is a test of recognition memory for unfamiliar faces. A short version of this test was used, which consists of the presentation of 25 faces at a rate of 1 picture every 3 seconds, and the participant is

required to evaluate the presented face as “pleasant” or “unpleasant.” Subsequently the participants are presented with 25 pairs of faces and are asked to identify the previously presented face from each pair. The total number of faces correctly recognized is recorded.

Working Memory Index (WMI) from the Wechsler Adult Intelligence Scale (WAIS-III)<sup>30</sup> is an index of working memory function derived from 3 of the WAIS-III subtests: arithmetic, digit span, and letter-number sequencing. The arithmetic subtest involves the verbal presentation of 16 mental arithmetic problems. The digit span subtest consists of 2 subparts: forward and backward digit span and assesses immediate auditory span, freedom from distraction, and executive function. The letter-number sequencing subtest involves ordering numbers and letters presented in an unordered sequence. Scaled scores for each subtest as well as a WMI are obtained.

Cognitive Failures Questionnaire (CFQ)<sup>31</sup> is a measure of self-reported deficits in the completion of simple everyday tasks which a person should normally be able to complete without error (eg, Do you fail to notice signposts on the road?). The questionnaire contains items on failures in attention, memory, perception, and motor function. Each incident is rated on a 4-point scale indicating its frequency. Total scores range from 0 to 100 and higher scores indicate a higher incidence of cognitive failures.

**Psychosocial Assessment.**—The participant’s mood, headache induced disability, and health-related QoL were measured using the following assessment tools:

*Mood, Disability, QoL.*—The Beck Depression Inventory (BDI-II)<sup>32</sup> is a self-report measure assessing the severity of depression in terms of the cognitive/affective, somatic, or behavioral symptoms of depression. Each item is rated between 0 and 3. Scores on all individual items are added to give the total BDI-II score. The scores 0-9, 10-18, 19-29, and 30-63 indicate no, mild, moderate, or severe depression, respectively.

The Hospital Anxiety and Depression Rating Scale (HADS)<sup>33</sup> is a self-report scale to detect depression and anxiety. It is composed of a 7-item subscale for depression and a 7-item subscale for anxiety. The individual items for each subscale are added to give a total score indicating overall anxiety (HADS-A) and

depression (HADS-D). The total score range for both subtests is 0-24, with scores above 8 and 11 indicating “possible” and “definite” “caseness” for anxiety/depression, respectively.

The Beck Hopelessness Scale (BHS)<sup>34</sup> is a self-report inventory measuring 3 major aspects of hopelessness: feelings about the future, loss of motivation, and expectations. The items consist of statements with which the respondent agrees or disagrees. Scores of 0-3, 4-8, 9-14, and 15-20 indicate minimal, mild, moderate, and severe hopelessness, respectively.

The Migraine Disability Assessment Scale (MIDAS)<sup>35</sup> is a questionnaire assessing disability due to headache. The MIDAS quantifies the impact of the headache on a patient’s personal life and occupation. The total score indicates the level of disability, falling within 1 of the 4 MIDAS grades: I, II, III, and IV, indicating little/no (total: 5 or less), mild (total: 6-10), moderate (total: 11-20), and severe (total: 21 or more) disability respectively.

The Headache Impact Test (HIT-6)<sup>36</sup> is a questionnaire assessing the impact of the headache on a patient’s ability to function in his/her daily life. Each item has a frequency response and is assigned an item category weight (6, 8, 10, 11, and 13). All item category weights are summed to form the total score indicating little/no impact (total: 49 or less), some impact (total: 50-55), substantial impact (total: 56-59), or very severe impact (total: 60 or more).

EuroQoL (EQ5D)<sup>37</sup> is a questionnaire covering 5 dimensions of QoL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The subscores can be combined to give a summary index value of 0-1. The EQ5D also includes a visual analog scale or thermometer for rating “current health state.” Lower scores represent poorer QoL for both parts of the test.

The Scales for Outcomes in Parkinson’s disease – Autonomic (SCOPA-AUT)<sup>38</sup> is a questionnaire assessing autonomic symptoms in 6 categories: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual dysfunction. Each item measures the presence of a specific autonomic problem, and is rated between 0 and 3 on its frequency. The scale gives a total score ranging from 0 to 78 with higher scores indicating more autonomic symptoms.

**Statistical Analyses.**—The analyses were conducted using IBM SPSS (Statistical Package for the Social Sciences, Armonk, NY, USA). Chi-square test of association was used to report frequencies of data for descriptive purposes, and the inferential analyses included a series of multivariate analyses of variance (MANOVAs). The independent variable was group (HC vs ECH vs CCH) and the dependent variables were the cognitive and psychosocial assessment measures. Where necessary, Tukey test was used for post hoc analysis. Pearson product-moment correlation coefficient was used for subsequent correlation analyses.

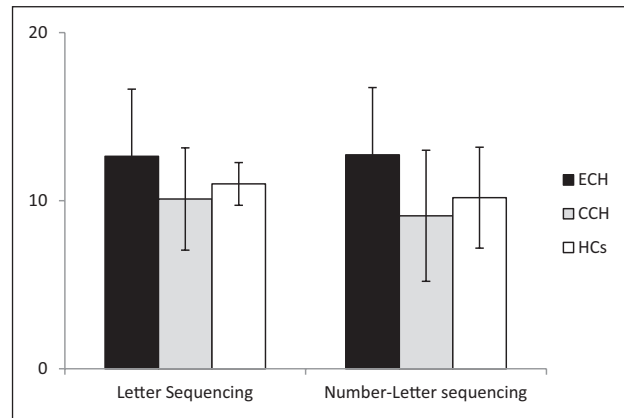
## RESULTS

There were no statistically significant differences in key demographic variables between the 3 groups ( $P > .05$ ), except for gender (see Table 1). The headache groups did not differ in terms of key clinical variables including age of onset, disease duration, or side of CH ( $P > .05$ ) (see Table 1).

**Cognitive Function.**—Three MANOVAs were performed to compare the 3 groups in terms of intelligence, executive functioning, and memory. The mean and standard deviations for each group and the results of the analyses are presented in Table 2.

*Measures of Intelligence.*—Both the current IQ and estimates of premorbid IQ for the 2 headache groups were in the “average range,” with no discrepancy between the 2 measures. For the HCs, current IQ was in the superior range and estimated premorbid IQ was in the high average range. There were no statistically significant differences between the 3 groups in measures of current IQ (WASI-FSIQ:  $F[2,29] = 3.130$ ,  $P = .059$ ), estimated premorbid IQ (NART-FSIQ:  $F[2,29] = 0.968$ ,  $P = .392$ ), or global cognitive functioning (MMSE:  $F[2,29] = 1.660$ ,  $P = .208$ ) (see Table 2).

*Measures of Executive Functioning.*—Executive functioning was measured using subtests of the TMT, VF, and Stroop. The MANOVA results yielded no statistically significant differences between the 3 groups on any of the measures (see Table 2), except on the letter sequencing and number-letter switching subtests of the TMT ( $F[2,27] = 4.492$ ,  $P = .021$  and  $F[2,27] = 3.416$ ,  $P = .048$  respectively). Following a



**Fig 1.**—Means and standard errors for patients with episodic and chronic cluster headache and healthy controls on 2 subtests of the Trail Making Test. HCs = healthy controls; ECH = episodic cluster headache; CCH = chronic cluster headache.

Bonferroni correction, setting alpha at 0.001, these statistical significances remained.

Post hoc comparisons using Tukey showed that these significant results were due to the difference in the means of the HCs and ECH patients with the latter group performing worse ( $P < .05$  on both tests) (see Fig. 1).

Interestingly, the ECH patients performed poorer on most subtests of TMT than CCH patients, although the differences did not reach significance (see Table 2).

*Measures of Memory Function.*—Memory function was assessed using the CVLT-II for verbal episodic memory, WAIS-III subtests for working memory, Warrington SRMF for non-verbal episodic memory, and CFQ for subjective memory. There were no statistically significant differences between the 3 groups on the CVLT-II and the arithmetic subtest of the WAIS-III WMI (see Table 2). There were group differences on the other 2 subtests of WAIS-III, the Warrington SRMF, and the CFQ (see Table 2 and Fig. 2). These statistical differences remained following a Bonferroni correction to account for the multiple comparisons.

Post hoc analyses of the WAIS-III subtests using Tukey's test showed a statistically significant difference in the mean scores for HCs and both ECH and CCH patients ( $P < .05$ ) (see Fig. 2a). On the letter-

**Table 2.—Means and Standard Deviations for the Measures of Intelligence, Executive Function and Memory Function**

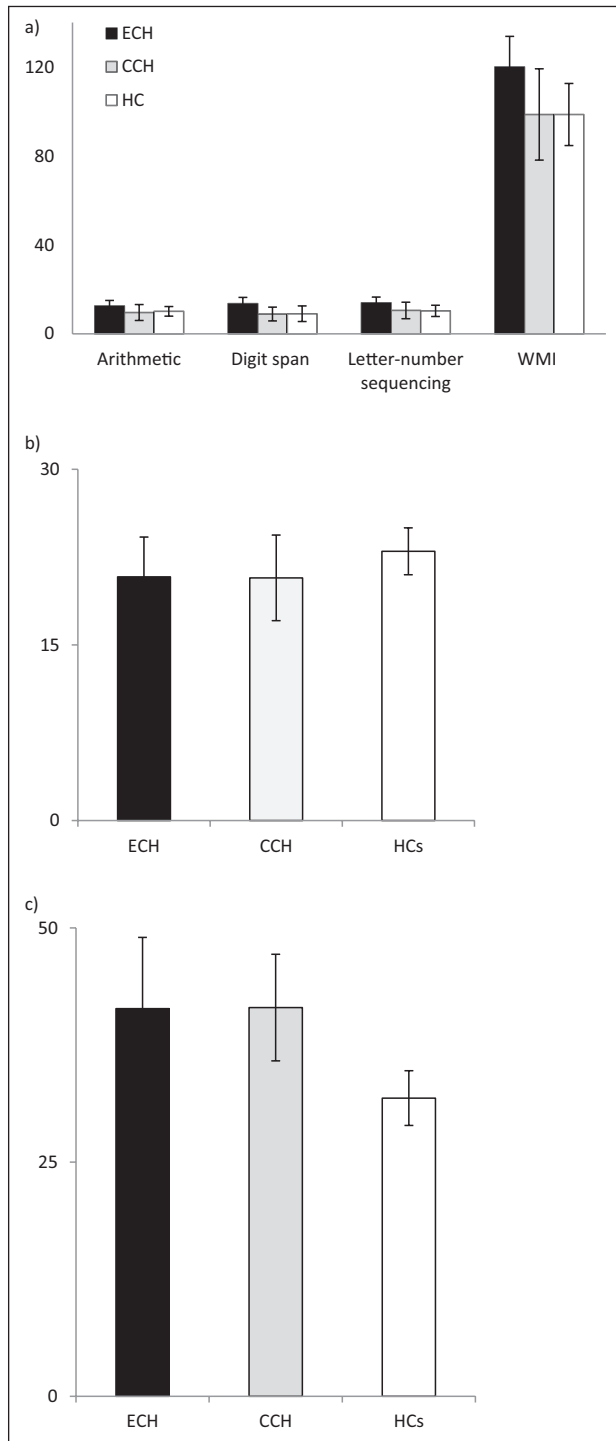
	HCs	ECH	CCH	<i>P</i>
Measures of intelligence				
WASI –full-scale IQ	124 ± 7.44	112.11 ± 15.42	114.27 ± 12.56	.059
NART –full-scale IQ	118.33 ± 6.47	112.91 ± 7.70	114.55 ± 9.18	.392
Mini Mental State Examination	29.00 ± 1.13	28.18 ± 1.66	29.36 ± 1.03	.208
Measures of executive function (D-KEFS)				
TMT scaled scores				
Visual scanning	11.45 ± 2.07	10.70 ± 2.50	9.09 ± 3.08	.169
Number sequencing	11.91 ± 2.17	11.30 ± 1.77	11.91 ± 1.45	.524
Letter sequencing	12.64 ± 1.86	10.10 ± 3.04	11.00 ± 1.27	.021*
Number-letter switching	12.73 ± 1.49	9.10 ± 3.90	10.18 ± 3.00	.048*
Motor speed	11.64 ± 1.29	10.10 ± 3.51	10.55 ± 1.57	.238
Letter-number switching vs letter sequencing	10.09 ± 1.14	8.56 ± 3.245	9.36 ± 2.157	.312
Verbal fluency scaled scores				
Letter	13.33 ± 3.73	11.56 ± 4.50	8.82 ± 3.82	.077
Category	12.25 ± 3.42	11.22 ± 4.21	10.73 ± 4.20	.856
Category switching	11.83 ± 3.49	11.78 ± 4.60	10.27 ± 2.72	.625
Color-word interference test scaled scores				
Color naming	10.10 ± 2.89	8.70 ± 1.95	8.36 ± 2.84	.315
Word reading	11.55 ± 2.34	9.10 ± 3.35	10.00 ± 2.15	.265
Inhibition	13.27 ± 2.24	10.80 ± 2.39	10.27 ± 3.55	.070
Inhibition/switching	12.45 ± 2.58	10.60 ± 2.50	11.45 ± 2.12	.493
Inhibition vs color naming	13.18 ± 1.94	12.11 ± 2.26	11.73 ± 2.69	.303
Measures of memory function				
CVLT-II raw scores				
Trial 1	6.46 ± 1.81	6.20 ± 2.25	6.64 ± 2.54	.704
Trial 1-5	55.09 ± 11.14	50.00 ± 10.93	49.18 ± 18.36	.620
Short delay-free recall	12.09 ± 2.63	10.11 ± 2.47	9.00 ± 5.35	.224
Short delay-cued recall	12.90 ± 2.73	11.33 ± 2.50	9.91 ± 5.45	.246
Long delay-free recall	12.64 ± 2.50	11.30 ± 2.71	9.36 ± 6.31	.216
Long delay-cued recall	12.73 ± 2.10	11.40 ± 2.80	10.09 ± 5.00	.228
Recognition-hits	15.18 ± 1.25	14.10 ± 2.18	13.55 ± 2.84	.192
Recognition-false positives	1.27 ± 1.27	1.80 ± 1.87	2.91 ± 3.20	.434
WAIS-III Working Memory Index (WMI) subtests scaled scores				
Arithmetic	12.50 ± 2.51	9.56 ± 3.58	10.10 ± 2.17	.129
Digit span	13.58 ± 2.81	8.90 ± 3.10	9.00 ± 3.50	.011*
Letter-number sequencing	13.92 ± 2.61	10.50 ± 3.70	10.30 ± 2.54	.025*
Working Memory Index	120.00 ± 13.78	98.63 ± 20.52	98.60 ± 13.96	.019*
Warrington Short Recognition Memory for Faces				
Correct responses (max25)	23.00 ± 2.00	20.82 ± 3.40	20.73 ± 3.66	.050*
Cognitive Failures Questionnaire				
Cognitive Failures Questionnaire	31.83 ± 10.11	41.38 ± 21.51	41.50 ± 18.27	.009*

CCH = chronic cluster headache; ECH = episodic cluster headache; HCs = healthy controls; NART = National Adult Reading Test; WASI = Wechsler Abbreviated Scale of Intelligence; \**P* < .05.

number sequencing, only the CCH group scored significantly lower than HCs (*P* < .05), and the difference between HCs and the ECH group was not (*P* = .07). On the WMI subtest, the ECH group scored significantly lower than the HCs (*P* < .05), and the difference between HC and CCH groups just missed significance (*P* = .06). For both of these subtests, the

headache groups did not differ from each other (*P* > .05) (see Fig. 2a).

On the Warrington SRMF, post-hoc tests showed that the differences between the 3 groups were not statistically significant (*P* < .05). The 3 means were homogenous (see Fig. 2b). On the CFQ, the HC means were significantly lower (less cognitive fail-



**Fig 2.**—Mean and standard error for patients with episodic and chronic cluster headache and healthy controls on tests assessing memory. (a) WAIS-III Working Memory Index subtests; (b) Warrington Short Recognition Memory for Faces; (c) Cognitive Failures Questionnaire. HCs = healthy controls; ECH = episodic cluster headache; CCH = chronic cluster headache; WAIS-III = Wechsler Adult Intelligence Scale III; WMI = Working Memory Index.

ures) than CCH ( $P < .05$ ) but not the ECH patients ( $P > .05$ ) (see Fig. 2c). The CCH group exhibited higher scores showing more cognitive failures, followed by ECH patients and then HCs (see Table 2).

**Psychosocial Function.**—Two separate MANOVAs were conducted on measures of mood, disability, and QoL. The first one examined differences in mood between the 3 groups, and the second analysis evaluated differences in disease impact and QoL. The descriptive results and their significant values are provided in Table 3.

*Measures of Mood, Disability, and QoL.*—The first analysis showed significant group differences on all measures of mood and autonomic dysfunction: BDI-II ( $F[2,25] = 18.482, P = .000$ ), HADS-A ( $F[2,25] = 5.497, P = .011$ ), HADS-D ( $F[2,25] = 19.140, P = .000$ ), BHS ( $F[2,25] = 9.358, P = .000$ ), and SCOPA-AUT ( $F[2,25] = 9.931, P = .000$ ). These statistically significant differences revealed the same pattern: patients with CCH had the highest scores on all of the measures, followed by ECH, and then the HCs (see Fig. 3a). When alpha was adjusted ( $P = .001$ ), these statistically significant differences remained.

A post hoc Tukey test showed that means for HCs and the ECH group, and HCs and CCH patients were significantly different on BHS, BDI-II, and HADS-D, with the patients scoring worse on all measures (all  $P < .005$ ). Post hoc comparisons of means on HADS-A showed a statistically significant difference only between HCs and patients with CCH ( $P < .05$ ), but not the ECH group ( $P > .05$ ). Similarly, post hoc analysis of means on SCOPA-AUT showed statistically significant differences between the CCH and HCs groups, and CCH and ECH groups (all  $P < .05$ ).

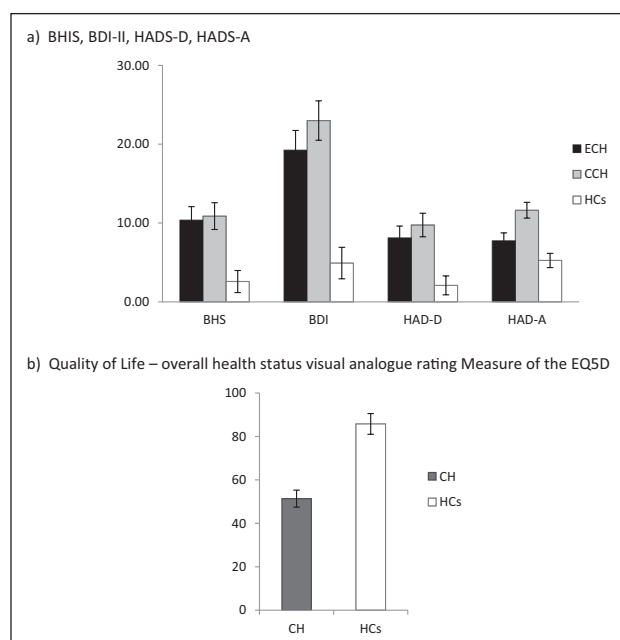
None of the HCs scored in the moderate or severe depression range on the BDI-II. In contrast, 35% of the ECH and 44% of the CCH groups scored in the moderately depressed range, and 25% of the ECH group and 22% of the CCH patients scored in the severe depression range. This difference between the 3 groups was statistically significant, indicating that a significantly higher proportion of the patients with ECH or CCH experienced moderate or severe depression compared with the HCs ( $\chi^2[2,29] = 12.541, P < .005$ ).



**Table 3.—Means and Standard Deviations for the Measures of Mood, Disability, and Quality of Life**

	HC	ECH	CCH	<i>P</i>
BDI-II	4.92 ± 2.811	19.25 ± 10.74	22.78 ± 6.76	.0001*
HADS-A	5.25 ± 2.864	7.75 ± 6.07	11.63 ± 3.70	.011*
HADS-D	2.08 ± 1.240	8.13 ± 4.02	9.75 ± 3.54	.0001*
BHS	2.58 ± 3.260	10.38 ± 6.12	11.67 ± 5.70	.001*
SCOPA-AUT	6.42 ± 4.209	10 ± 3.703	18.88 ± 9.72	.001*
MIDAS		71.40 ± 59.54	53.13 ± 37.10	.126
HIT-6		64.60 ± 11.86	64.60 ± 4.81	.875
EQ5D- health status	0.89 ± 0.12	1.85 ± 3.82	0.31 ± 0.32	.325
EQ5D- thermometer	85.75 ± 9.29	44.90 ± 23.84	56.00 ± 13.79	.344

A = anxiety; BDI-II = Beck Depression Inventory II; BHS = Beck Hopelessness Scale; CCH = chronic cluster headache; D = depression; ECH = episodic cluster headache; EQ5D = EuroQoL quality of life scale; HADS = Hospital Anxiety and Depression rating scale; HCs = healthy controls; HIT-6 = Headache Impact Test-6; MIDAS = Migraine Disability Assessment Scale; SCOPA-AUT; Scales for Outcomes in Parkinson's disease – Autonomic; \**P* < .05.



**Fig 3.—Means and standard errors for (a) hopelessness (BHS), depression (BDI-II and HADS-D) and anxiety (HADS-A) and (b) quality of life for the patients with chronic or episodic cluster headache and healthy controls. BHS = Beck Hopelessness Scale; BDI-II = Beck Depression Inventory II; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression; EQ5D = EuroQoL quality of life measure; ECH = episodic cluster headache; CCH = chronic cluster headache; CH = cluster headache; HCs = healthy controls.**

Similarly, on the HADS-D, while none of the HCs achieved “caseness” indicating definite depression, 38% of the patients with ECH and 38% of the CCH patients did so. The association between group (HC, ECH, CCH) and “caseness” (yes vs no) for depression on the HADS-D approached significance ( $\chi^2[2,27] = 5.304, P = .071$ ). However, a significantly higher proportion of the patients with ECH or CCH achieved “caseness” for anxiety on HADS-A than the HCs. ( $\chi^2[2,28] = 9.307, P < .05$ ). One participant in the HCs group (8%), 38% of the ECH group, and 75% of the CCH patients achieved “caseness” for anxiety as measured on HADS-A.

The second analysis revealed no differences in QoL between the 3 groups (EQ5D health state:  $F[1,13] = 1.049, P = .325$ ; EQ5D thermometer:  $F[1,13] = 0.963, P = .344$ ). Similarly, there were no group differences between the headache groups concerning the impact of their headache (HIT-6:  $F[1,13] = 0.026, P = .875$ ) or headache-related disability (MIDAS:  $F[1,13] = 2.674, P = .126$ ). We then combined the 2 headache groups, to compare QoL between HCs and CH patients. The results revealed no difference in the EQ5D health state ( $F[1,28] = 0.054, P = .818$ ) but showed a statistically significant group difference in the EQ5D visual analog scale rating of overall health status ( $F[1,28]: 31.104, P = .001$ ), which

as expected was higher in HCs ( $85.75 \pm 9.29$ ) than CH patients ( $51.39 \pm 19.86$ ) (see Fig. 3b).

**Correlational Analysis.**—A number of correlational analyses were carried out using Pearson correlation coefficient, to examine the relationship between demographic and clinical variables (age, age of onset, disease duration, years of education, side of CH) and participant's mood, disease impact, QoL (as listed in Table 3) and cognitive test results listed in Table 2. There was a statistically significant negative correlation between age and MIDAS ( $r = -0.806$ ,  $P < .005$ ), and age and BHS ( $r = -0.424$ ,  $P < .05$ ). Disease duration correlated negatively and statistically significantly with WASI FSIQ ( $r = -0.459$ ,  $P < .05$ ) and also with 2 measures of the CVLT-II (negatively with the long delay free recall:  $r = -0.463$ ,  $P < .05$ ; and positively with false positives on the recognition test:  $r = 0.527$ ,  $P < .05$ ). Furthermore, there was a negative correlation between age at onset and MIDAS ( $r = -0.466$ ,  $P < .05$ ), and years of education and the category subtest of VF ( $r = -0.414$ ,  $P < .05$ ). None of the other correlations were statistically significant or noteworthy. It was not possible to statistically adjust the alpha to account for multiple comparisons due to the sample size. Thus these should be interpreted with caution.

## DISCUSSION

There is some evidence available that illustrate the negative impact of CH. However, to our knowledge, there are no data available that compare patients with ECH and those with CCH with HCs on measures of QoL, daily functioning, mood, and cognition, which was the aim of this study.

**Cognitive Function in CH.**—We assessed intelligence, executive function, and memory. The results showed comparable scores on a global measure of cognitive ability, and premorbid and current IQ for CH patients, and age-matched HCs, and no statistically significant differences were found on most measures of executive function. However, patients with CH performed worse on some of the working memory and TMT subtests and reported more cognitive failures.

In terms of intelligence, the patients in our sample did not differ significantly from HCs on measures of IQ or global cognitive functioning. The

premorbid and current IQ in the patient groups was in the average range, and although the IQ of HCs was in the superior/high average ranges, they did not differ statistically significantly from patients with CH.

The only deficit in executive function shown by patients with CH relative to HCs was for the letter sequencing and number-letter switching subtests of TMT. However, conversion of the scores into scaled scores based on the population means for their respective age groups did not show a great variation. They indicated that the 3 groups (HC, ECH, CCH) had scaled scores of 12, 10, and 11 on the letter sequencing and 12, 9, and 10 on the number-letter switching subtest. Furthermore, interestingly, patients with ECH performed worse than those with CCH on most subtests, but the differences were small and therefore not statistically significant. These differences could be indicative of reduced mental flexibility in patients with CH, particularly those with ECH. A trend was also observed for the letter fluency subtest of the D-KEFS, with CCH patients performing worse than the 2 other groups. Future results from a larger sample would clarify if this difference can reach significance. The mean scaled scores of all groups fell within the average to high average performance range on the measures of executive function, and were mostly not statistically significantly different from HCs. In addition, since the tests administered tapped various aspects of executive function, this aspect of cognitive function can be considered intact in both ECH and CCH.

Overall, these results confirm previous research in showing no major deficits in the executive function of patients with ECH<sup>11</sup> and CCH,<sup>18</sup> and extend this yet further by comparing the performance of both groups on the same measures. This study also provides unique data on measures of memory, particularly the working memory in patients with ECH and CCH. Our results revealed that CCH patients showed greater impairment on tests that required information to be re-ordered (letter-number sequencing), ie, necessitating manipulation of information held in working memory, while the ECH patients performed statistically significantly worse on the WMI of the WAIS-III, which provides a general measure of working memory.

The WMI for the HCs was 120, compared with 98 for the 2 CH groups. In terms of clinical significance, the mean scaled scores indicated average performance for all working memory subtests in the 2 headache groups, while performance in the HC group was found to be within a high average range. Therefore, the observed statistical difference in working memory function between the 2 patient groups and the HC group is not suggestive of significant clinical deficits since their performance remained in the average range despite being significantly lower than HCs statistically. In addition, the results of the 3 groups, including the headache groups, do not vary greatly from the population mean and standard deviation of the scaled scores of the individual subtests (10 and 3, respectively) or the WMI (100 and 15, respectively).

However, when patients were asked to rate the severity of their own cognitive failures, patients with CCH reported higher cognitive failures than the ECH patients, and statistically significantly higher failures than HCs. Although this may be a true reflection of greater deficits in patients with CCH which would be consistent with their poorer performance on working memory tests, an alternative explanation would be that CCH patients are less confident about their mnemonic abilities compared with ECH patients, especially when we consider the higher levels of anxiety in patients with CCH. Furthermore, contrary to previous reports of reduced verbal memory function in CH,<sup>11</sup> our results did not show any statistically significant differences between either of the headache groups and HC on measures of short- and long-term episodic verbal memory.

This study provides a comprehensive account of cognitive function in patients with CH, both ECH and CCH. The results indicate that intelligence, executive function, and episodic memory are largely intact in patients with CH, and where deficits are observed, they are of little clinical relevance and do not impair the normal cognitive functioning of the patients. Furthermore, although there has been evidence suggesting a pivotal role of the hypothalamus in the development of CH,<sup>21,39-42</sup> given the pure neuropsychological nature of this study, however, no statement can be made on the neural basis of the observed deficits. This remains to be investigated in future studies.

**Psychosocial Function in CH.**—We investigated the impact of CH on various measures of mood and autonomic symptoms, disability, and QoL.

In line with previous studies, our results showed that patients with CH (both ECH and CCH) had increased rates of depression, anxiety, hopelessness, and autonomic symptoms relative to HCs.<sup>8,9,12,13</sup> Interestingly, although the number of patients achieving “caseness” for depression was identical in both headache groups (38%), a larger proportion of the CCH patients (75%) achieved “caseness” for anxiety than the ECH group (38%). Since CCH patients do not experience a period of remission, the higher incidence of anxiety in this group is perhaps a reflection of the implications of having a chronic disorder. The SCOPA-AUT, which is a measure mainly used for assessing autonomic symptoms of patients with Parkinson’s disease was used to identify the presence of any autonomic symptoms in this sample and to identify if the headache frequency affected the severity of these. Interestingly, the findings did show that patients with CCH experienced significantly more autonomic symptoms not only than HCs but also than ECH sufferers, while patients with ECHs did not show a statistically significant difference from HCs. The unpredictable and ongoing nature of the headache attacks experienced in CCH can have a great impact on simple activities of daily living and the anxiety caused can potentially create a sense of “fear” affecting planning of events, socializing, productivity, and integration in activities.

We also investigated the level of disability caused by CH by examining the patients’ ability to function in daily activities (HIT-6) and on personal and occupational roles (MIDAS), and found no statistically significant differences between patients with CCH and those with ECH. Conversely, in a recent study, Jürgens and colleagues<sup>8</sup> examined disability caused by headache in 130 participants using the Hospital Headache Disability Inventory. They compared disability in patients with CCH, ECH in a bout and ECH in remission, and patients’ with migraine. Their results showed that the impact of headache was greatest for CCH patients, followed by ECH in a bout, ECH in remission, and then those with migraine.

Since the participants in our sample were recruited at the tertiary headache clinic, they would be expected to display severe cases of headache and thus the lack of difference between the 2 headache groups concerning disability is not surprising. Although the participants with ECH in our sample were assessed during an active headache attack and their scores may only be applicable to disability as perceived at the time, the findings illustrate that disability caused by CH may be similar in both episodic and chronic types at the time of the attack. The mean results on the HIT-6 were comparable between the 2 headache groups, and although the mean MIDAS scores show that ECH patients reported greater disability than CCH patients, the difference was not significant.

The correlational analysis showed that younger patients and those diagnosed at an earlier age reported higher disease impact on personal and occupational roles. This highlights the importance of considering interpersonal and demographic details and how they influence the patients' ability to cope with their illness.

Interestingly, contrary to previous literature,<sup>6,7</sup> despite severe disability reported by both headache groups, there were no differences in QoL and health status (EQ5D) of the 2 headache groups relative to HCs. However, when the ECH and CCH patients were combined to form 1 group, compared with HCs, they showed significantly lower current health status. Since the HCs were made up of the partners of our patients, it is possible that having a spouse with a neurological condition may have affected their QoL and thus explains the similarity in their reported QoL when compared with ECH and CCH patients separately.

## CONCLUSION

This study provides neuropsychological data on the cognitive profile and information about mood, disability, and QoL, and patients with episodic and chronic forms of CH from 1 specialist clinic.

A major limitation of this study is that of sample size, particularly given that a number of multiple analyses were conducted. Although it is important to note that multiple testing increases the potential risk of committing a type I error, in this case of finding a

difference in the measures between the groups when no such difference exists, the statistically significant results found here were usually highly significant. Given that multiple comparisons were made to test the hypotheses, a Bonferroni correction was applied to lower the risks of type I error. Following application of such a correction, all of the statistically significant results remained unchanged. Inevitably with a larger sample size, it is possible that further significant results may have been discovered; however, given the rarity of CH, especially CH in the absence of any other neurological or psychological diagnosis, the current sample size is considered adequate. Patients normally seen at tertiary settings usually have very severe health conditions, and a great number of patients seen at this headache clinic had multiple headache diagnoses. Therefore, for the purposes of this study, only patients with pure ECH or CCH were included. Moreover, the majority of previous studies investigating psychosocial factors and particularly those investigating cognitive function in CH have had relatively small samples.<sup>7-12,20,21</sup> Nevertheless, further studies with larger samples are encouraged. Inclusion of larger samples and controlling for medication effects on cognition could determine if the observed effects are actually due to CH rather than possibly side effects of medication.

Nonetheless, the results presented here highlight the severe impact of CH on the mental health of both patients with ECH and CCH compared with HCs. It particularly highlights the high incidence of anxiety disorders in this painful and unpredictable condition. The results also indicate poor QoL and the severely disabling nature of CH. Despite the impairment in QoL and high levels of health-related disability and psychiatric comorbidity found in CH, cognitive function remained largely intact in both ECH and CCH patients included in this sample, thus confirming previous reports of intact cognition in CH patients.

The high levels of disability and mood disturbance in CH warrants direct management of these problems in clinical practice. Anti-depressant medication and/or psychotherapy to help patients come to terms with the disabling nature of their CHs may both prove of value. Despite some differences between CCH and ECH found in this study, the results indi-

cate that CH can have a severely disabling and negative influence on various aspects of living and general well-being regardless of the frequency of the attacks.

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