Psychiatry Research 186 (2011) 367–372

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Psychomotor function and response inhibition in chronic fatigue syndrome

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ARTICLE INFO

Article history:
Received 30 June 2009
Received in revised form 20 July 2010
Accepted 23 July 2010

Keywords:
Chronic fatigue
Cognition
Executive function
Functional disorder
Movement
Somatoform disorder
Psychomotor performance

ABSTRACT

Most research points to cognitive slowing in chronic fatigue syndrome (CFS), although there have been negative reports. The present study is one of few that examines fine motor processing and the inhibition of automatic responses in a well-characterised CFS population. A total of 35 female CFS patients without current major depression and 25 female controls performed two computerised figure-copying tasks. The cognitive and fine motor processing of visual–spatial information was measured by recording reaction time (RT) and movement time (MT), respectively. The inhibition of automatic responses was assessed by introducing 'conflicting patterns' (i.e., patterns that were difficult to draw from the preferred left to right). A multivariate general linear model was adopted for the statistical analysis of the movement recordings. As a result, CFS was significantly associated with longer RT and MT in the pooled and in the task-specific analyses. However, there was no interaction between disease status and conflicting character of the patterns. In conclusion, these performance data on the figure-copying tasks provide confirmatory evidence for psychomotor slowing in CFS, but not for a disturbed inhibition of automatic responses. Computerised figure-copying tasks may be promising tools for use in neurobiological research and clinical trials in CFS.

1. Introduction

Chronic fatigue syndrome (CFS) is characterised by unexplained, profound disabling and long-lasting fatigue that is of new or definite onset, which is not the result of ongoing exertion and also that it is not substantially alleviated by rest. The fatigue must be accompanied by at least four or more of the following case-defining symptoms during at least 6 months of consecutive illness: sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, post-exertional malaise, un-refreshing sleep, headaches and impaired memory or concentration (Fukuda et al., 1994). Although several aetiological factors have been identified, the underlying pathophysiology of CFS remains unclear (Prins et al., 2006).

The majority of patients with CFS complain of deficiencies in attention, concentration and memory abilities (Afari and Buchwald, 2003). Studies in CFS have described positive correlations between subjective complaints of mental fatigue and objective measurements of cognitive impairment (Capuron et al., 2006), as well as a positive correlation between cognitive impairment and functional deficits (Christodoulou et al., 1998; Vercoulen et al., 1998). Although, in general, neuropsychological studies have produced inconsistent results, slowed processing speed, impaired working memory and poor learning of information are prominent features of cognitive dysfunction in CFS (Michiels and Cluydts, 2001). Conflicting reports may reflect sample selection bias, diagnostic heterogeneity, co-morbid psychiatric disorders, medication usage and variability among the types of neuropsychological testing batteries (Michiels and Cluydts, 2001; Majer et al., 2008).

As to psychomotor functioning in CFS, the focus of the present study, several earlier studies reported prolonged simple or choice reaction times (RTs) (Scheffers et al., 1992; Smith et al., 1993; Marshall et al., 1996, 1997; Vercoulen et al., 1998; Majer et al., 2008), whereas others failed to find such delays (Grafman et al., 1993; Fiedler et al., 1996). Moreover, only few studies examined fine motor processing or inhibition of automatic responses in CFS (Michiels and Cluydts, 2001). In a recent study, we compared psychomotor function between 38 well-diagnosed CFS patients, 32 major depressive disorder (MDD) patients and 38 healthy controls by means of computerised copying tasks differing in complexity (Schrijvers et al.,

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doi:10.1016/j.psychres.2010.07.022

2009). In these tasks, figures were presented on a computer screen and the subjects were instructed to copy them into the squares of a sheet of paper that was placed on the digitiser. As a result, both patient groups demonstrated an overall fine motor slowing, with the motor component being more affected in the MDD patients than in the CFS patients, while both groups showed similar cognitive impairments. This might reflect the striatal dysfunctions reported in both conditions (Schrijvers et al., 2009).

These computerised copying tasks have earlier been shown to be suitable to determine the degree and nature of psychomotor retardation in MDD (Sabbe et al., 1996; Pier et al., 2004; Schrijvers et al., 2008), anorexia nervosa (Pieters et al., 2003, 2006) and schizophrenia (Jogems-Kosterman et al., 2001, 2006). The use of this method allows a distinction to be made between the cognitive and fine motor processes that occur in response to visual stimuli. In addition, by manipulating the complexity of the figures to be copied, the processing load of the cognitive task components can be increased. Furthermore, to examine the inhibition of automatic responses, 'conflicting patterns' can be introduced. More precisely, our writing and drawing movements appear to be governed by certain graphic rules. These rules specify preferences with respect to starting points, stroke directions and stroke sequences (Thomassen and Tibosch, 1991). In the preferred condition, participants have to inhibit a more or less automatic response. Thus, by comparing patterns that are conflicting with these rules and 'non-conflicting' patterns, the inhibition of automatic responses can be quantified (Jogems-Kosterman et al., 2001).

The main objective of the current study was to further examine the pattern of psychomotor slowing in a well-characterised tertiary sample of CFS patients by means of computerised copying tasks, with a special focus on the inhibition of automatic responses. It was hypothesised that cognitive and fine motor processing of visual–spatial information would be slowed in CFS patients, as compared with healthy control individuals. In addition, we explored the effects of conflicting patterns and of increasing task complexity.

2. Methods

2.1. Subjects

Adult patients attending the CFS clinic of the Department of Internal Medicine of the University Hospital of Antwerp, Belgium, were invited by letter to participate in the study. Consistent with reports in the literature (Jason et al., 1999), the majority of the CFS patients being treated at the clinic were women, with few men responding to our invitation. For homogeneity of the study population, we, hence, decided to include only female patients and controls. An experienced internist (GM) diagnosed CFS according to the Centre for Disease Control Criteria (Fukuda et al., 1994). All patients underwent serial physical examinations and laboratory evaluations; no alternative medical diagnosis could be established. Eventually, 35 patients with CFS were included in the study. Healthy female volunteers without a past history of CFS were recruited by an advertisement in the Antwerp University Hospital; 25 controls matched for age and educational level were included. Five levels of education were considered in accordance with the Belgian educational system. Although not mandatory, all participants were requested to refrain from taking benzodiazepines the evening or night before testing. The patient group was larger to allow a secondary within-group analysis of potentially influencing clinical variables. The study was carried out consistent with the latest version of the Helsinki Declaration and was approved by the Medical Ethics Committee of the Antwerp University Hospital. All participants were over 18 years of age and gave their written, informed consent. All control individuals and patients also participated in the previously mentioned study by Schrijvers et al. (2009).

2.2. Interviews and questionnaires

All the participants were interviewed by a trained psychiatrist (FVDE) in accordance with the Dutch version of the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV) Axis I Disorders, version 2.0 (van Groenestijn et al., 1999). We adopted the psychiatric exclusion criteria for CFS as formulated by the US Centers for Disease Control and Prevention (Fukuda et al., 1994), with three exceptions. First, to avoid a state effect of MDD on psychomotor outcomes, subjects meeting the criteria for a current major depressive episode according to DSM-IV (American Psychiatric Association, 1994) were excluded (two CFS patients). Second, a history of melancholic depression was not assessed systematically, because the Structured Clinical Interview for DSM-IV (SCID)-I/P does not provide a specification of melancholic features in the past and because it is difficult to assess this aspect retrospectively by means of an interview. Finally, one healthy control had suffered from anorexia nervosa in the past, but had been in complete remission for more than 5 years.

The validated and reliable 20-item Checklist Individual Strength (CIS) (Vercoulen et al., 1999) was used to measure the patients' perceived fatigue, concentration, motivation and physical activity.

2.3. Copying tasks

All tasks were administered with the aid of a PC, a WACOM digitiser and a pressure-sensitive pen (Maarse et al., 1988). The stimuli were presented on a computer screen. Examples of the patterns used in the copying tasks in this study are depicted in Fig. 1. In Task 1, conflicting patterns (i.e., patterns that were difficult to draw from the preferred left to right) were alternated with non-conflicting patterns obeying the preferences. Generally, the production rule to start at the left is favoured by most participants and, therefore, the conflict between the rules may not be that strong. The stimuli needed to be copied 24 times. Complexity (increasing processing load) differed depending on the number of segments in the patterns. In Task 2, conflicting and non-conflicting patterns were presented 48 times with a dot indicating the fixed starting point. This implied that the imposed starting point either corresponded to or deviated from the normal preference. This preference could be either strong (non-conflicting) or weaker (conflicting). The conflict in Task 2 is of a different order than in Task 1, because an externally imposed demand (to start at the dot) is in conflict with a natural tendency to start at the left. Therefore, the required inhibition of automatic responses is stronger in Task 2 than in Task 1.

The participants were instructed to copy the stimuli as fast and as accurately as possible inside pre-printed (3×4 cm) squares on a sheet of paper that was placed on the digitiser. As soon as they touched the (empty) start circle printed at the bottom left of each box, a stimulus appeared on the screen, which disappeared the moment they started drawing. After having drawn the figure, they were instructed to place the pen in the (filled) stop circle printed at the top right of each box. The pen-tip position was recorded with a 0.2-mm accuracy at a rate of 206 Hz. RT and movement time (MT) were recorded, with RT being defined as the interval between the onset of the stimulus presentation and the moment the pen touched the copy area and the pressure threshold was exceeded, and MT being defined as the interval between the moment the pressure threshold was exceeded inside the copy area and the end point of the final drawing movement.

2.4. Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 12.0. A multivariate general linear model (GLM) was used to examine the differences between patients and controls, with separate analyses for RT and MT. One-sided testing was used in this part of the statistical analysis because it was hypothesised that RT and MT would be significantly prolonged in CFS patients. In addition, a repeated-measures GLM was adopted for RT with disease status as between-subjects factor and the following within-subject factors: conflicting pattern and complexity in Task 1 and conflicting pattern in task 2. For every GLM, the Wilk's Lambda is reported. The following clinical variables were noted: past history of MDD, fibromyalgia, use of benzodiazepines and use of antidepressants. These variables were incorporated as fixed factors in the multivariate GLM. The possibly confounding effect of fibromyalgia and of the use of benzodiazepines and antidepressants was examined in the patient group only, since none of the controls suffered from fibromyalgia or used these medications. For the analysis of the sample characteristics, a chi-square analysis was applied to compare frequencies. Fisher's exact test was applied when necessary. If quantitative data failed to satisfy the assumptions for parametrical statistical analyses (independent samples *t*-test), they were analysed non-parametrically (Mann–Whitney *U* test). For all analyses, we adopted a P value of <0.05 as the level of significance; a P value of <0.1 is reported as a trend.

3. Results

3.1. Study group characteristics

The characteristics of the two study groups are presented in Table 1. All but one patient were unable to work because of chronic fatigue, whereas all controls had an active employment status. As expected, the item scores for the CIS were significantly higher in the patient group (Vercoulen et al., 1999). In accordance with previous studies (Afari and Buchwald, 2003), there was a higher frequency of the following conditions in the patient group: fibromyalgia; somatisation disorder; current anxiety disorder (specific phobia, $n=1$; social phobia, $n=1$; generalised anxiety disorder, $n=4$; panic disorder with or without agoraphobia, $n=4$; and anxiety not otherwise specified, $n=1$) and history of one or more major depressive episodes. The severity of the