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Clinical study

Response inhibition in patients with functional neurological symptom disorder

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ABSTRACT

Abnormal response inhibition has been demonstrated in psychogenic movement disorders (PMD) and is a plausible mechanism for other forms of functional neurological symptom disorder (FNSD), in which response inhibition has not yet been investigated. Response inhibition was therefore studied in patients with FNSD, including patients with psychogenic non-epileptic seizures (PNES), functional weakness (FW) or both. Twenty-nine patients with FNSD and 29 age and sex-matched healthy volunteers underwent a go-nogo task, a stop-signal reaction time (SSRT) task, and a negative priming flanker task. The Attentional Resource Allocation Scale, the Beck Depression Inventory and the Spielberger State and Trait Anxiety Inventory were also administered. Mean hit rates on nogo trials, miss rates on go signals and discriminability index were higher and go signal reaction times were significantly longer in the FNSD group than in healthy controls. The presence of FW was associated with increased hit rates on nogo trials, suggesting a bias toward responding to nogo signals rather than missed go signals. SSRT and negative priming were not significantly different from healthy controls. It is unclear whether impaired performance on the go-nogo task reflects dysfunctional inhibitory processes, disordered attention, or impaired ability to discriminate between stimuli.

1. Introduction

Functional neurological symptom disorder (FNSD) describes medically unexplained neurological symptoms that include functional weakness (FW), psychogenic movement disorder (PMD), psychogenic non-epileptic seizures (PNES) and a variety of less common manifestations such as functional blindness and other sensory symptoms [1,2]. Psychological factors are probably important, because symptoms may be preceded by conflicts or other stressors [3]. PMD describes unexplained involuntary movements such as tremor or dystonia, often seen in movement disorder clinics [4], while PNES describes events that simulate seizures but lack electroencephalographic correlates [5].

Appropriate inhibitory processes are necessary for behavioural control and are impaired in neuropsychological disorders such as attention deficit hyperactivity disorder and obsessive compulsive disorder [6,7]. It is plausible that inhibitory mechanisms may be abnormal in patients with FNSD, as they often involve excess or lack of movement. A common presentation is FW or "conversion paralysis", occurring in a distribution inconsistent with neuroanatomy and variable across repeated examinations. Plausibly, FW could be due to activation of inhibitory networks during attempted movement [8–10], but another functional magnetic resonance imaging (fMRI) study showed no evidence of activation of right frontal areas known to be involved in inhibition during a go-nogo task in a patient with conversion paralysis on testing the limb on the affected side [11]. Impaired response inhibition has however been demonstrated in PMD patients manifesting with positive motor symptoms such as tremor, dystonia and chorea [12], consistent with the idea that abnormal response inhibition might play a role where movements are excessive. In PNES, there may be limb movements reminiscent of tonic-clonic seizures, or impaired consciousness or collapse without increased motor activity [13], so it might be postulated that inhibitory mechanisms could be increased or decreased, depending on the phenomenology of the seizures. FNSD is associated with dissociation, and there is evidence of impaired cognitive inhibition in dissociative identity disorder, as demonstrated by reduced negative priming in a flanker task, when tested in a negative emotional context [14]. Our hypothesis, therefore, was that abnormal inhibition would be

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found in FNSD and that it might be decreased or increased depending on the phenomenology.

We studied response inhibition in patients with FNSD with PNES, FW, or a combination of the two and compared them to an age and sex matched sample of healthy controls using a go-nogo task, a stop-signal reaction time (SSRT) task [15] and a negative priming flanker task [16]. Psychometric tests of depression, anxiety and dissociation were assessed as potential covariates, because depression and anxiety are frequent comorbidities, and FNSD may be a form of dissociative disorder [17–20]. A secondary aim of the study was to explore differences between PNES and functional weakness, recognizing that there is considerable overlap between the two types of presentation of FNSD.

2. Methods

Patients with FNSD were recruited from the Neurology Department of Dunedin Hospital, and age- and sex-matched healthy control participants were recruited by advertisement. All patients had been examined and the diagnosis made by a senior neurologist. FW was diagnosed on the basis of weakness inconsistent with neuroanatomy and neurophysiology, characterised by "give-way", normal reflexes and normal neuroimaging. The diagnosis of PNES was based on the demonstration of normal electroencephalography (EEG) during typical attacks, recorded during inpatient video-EEG monitoring. Evidence of psychological dysfunction was not a necessary feature for inclusion in the study, consistent with changes in psychiatric classification in the Diagnostic and Statistical Manual V (DSM V) [21].

Each participant was tested in a single session lasting up to 90 min. All patients with functional weakness were symptomatic at the time of testing. Psychological questionnaires alternated with computer-based tests, to reduce fatigue. The order in which the tests were performed was counterbalanced across patients and administered in the same order for each patient's matched control whenever possible. All patients provided informed written consent and the study was approved by the Southern Regional Ethics Committee, New Zealand.

2.1. Psychometric battery

All participants completed the Edinburgh Handedness Inventory [22], the Attentional Resource Allocation Scale (ARAS) [19], the Beck Depression Inventory (BDI) [17] and Spielberger's State and Trait Anxiety Inventory (STAI-state and STAI-trait) [18]. The ARAS combines questions from the Dissociative Experiences Scale (DES) and the Tellegen Absorption Scale (TAS) [23,24], and attempts to provide a better tool to measure these phenomena. Higher scores would be expected in FNSD, based on previous findings of dissociative symptoms in these patients [25]. Anxiety was assessed using STAI, a 40 item questionnaire providing information both on the level of anxiety "at this moment" (state) and how the participant "generally feels" (trait) (Mind Garden, Inc.) [18,26].

2.2. Behavioural tasks

2.2.1. Go-nogo task

The go-nogo task was administered using E-Prime software (Psychology Software Tools, Pittsburgh, PA) [27]. Participants performed a choice reaction time task based on a visual stimulus on a computer display, either a circle or a square of 18 mm width or diameter, subtending a visual angle of 14° at a distance of 75 mm. Participants were instructed to press, as quickly as possible, the left response button with the left forefinger if the stimulus was a square or the right response button with the right forefinger if it was a circle. If the visual stimulus was accompanied by an auditory stimulus (a high pitched tone), the participant was instructed to withhold the response (nogo trials). Three blocks of 40 trials were performed, including 30% nogo trials. For each trial, a fixation cross was presented for 1 s, followed by the go stimulus with or without simultaneous presentation of the auditory stop stimulus. The go stimulus disappeared on pressing the response button and was replaced by the fixation cross in preparation for the next stimulus.

Dependent variables included: nogo hit rate (NGHR; false alarms; errors of comission), go-signal miss rate (GSMR; missed go trials; errors of omission), Go-signal hit rate (GSHR; correct response to go stimuli) and go-signal reaction time (GSRT). The results were analysed according to Signal Detection Theory [28,29]. Z scores were calculated for NGHR and GSHR and the discriminability index (d′) was calculated as: d′ = z (GSHR)-z (NGHR). A lower d′ represents more errors. The natural logarithm of beta, ln (beta), an index of bias, was calculated as:

$$\frac{[Z(NGHR)]^2 - [Z(GSHR)]^2}{2}$$

Values less than 1 reflect bias toward nogo hits and values greater than one reflect bias toward missed go signals [29]. Mean reaction times were determined after trimming the data by removal of outliers less or greater than 3 standard deviations from mean.

2.2.2. Stop signal reaction times

SSRT were determined using the STOP-IT software program of Verbruggen et al. (http://www.psy.vanderbilt.edu/faculty/logan/#stopit) [30]. In this paradigm, participants perform a choice reaction task based on a visual stimulus, a circle or a square, as in the go-nogo task. Similarly, the participant presses either the left response button with the left forefinger if the stimulus is a square or the right response button if it is a circle (diameter or width of stimuli 14 mm: stimuli subtended a visual angle of 11° at a viewing distance of 75 mm). The participant is instructed to withhold the response if the visual stimulus is accompanied by an auditory stimulus (a tone, heard in 25% of trials). The STOP-IT software uses a tracking procedure to adjust the stop signal delay during the experiment, so that subjects stop half of the responses [30].

The stop signal task is thought to examine a different aspect of movement inhibition to the go-nogo task in that a variable time delay between the go and the nogo stimuli occurs during the SSRT task, and in most cases, a response has been initiated before being halted (unlike in the go nogo task where a nogo response might never be initiated). For SSRT, the logic of a "horse race" model has been proposed in which there is a "go" process triggered by the visual stimulus, and a "stop" process triggered by the auditory stimulus [30]. Whichever process finishes first determines whether the response is successfully withheld or not. In the stop signal task, the delay between the stop and the go signal is varied in order to determine the SSRT, which is calculated by subtracting mean stop signal delay from the untrimmed mean RT, and represents the mean time to internally inhibit a response [30].

2.2.3. Negative priming

Negative priming (NP) was studied using a flanker task, modified from Dorahy et al. [31]. The participants were presented stimuli consisting of a row of three figures and instructed to read out the middle digit as quickly as possible. All digits were used, except for 7 and 0 to avoid the use of two syllable words, and the two outer digits [flankers] were identical to each other, but different to the middle digit. Letters were presented in Courier New, size 18 font, separated by single spaces and each digit subtending a

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