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A case-matched study of neurophysiological correlates to attention /working memory in people with somatic hypervigilance

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Title: A case-matched study of neurophysiological correlates to attention/working memory in people with somatic hypervigilance

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Abstract

Objective: Somatic hypervigilance describes a clinical presentation in which people report more, and more intense, bodily sensations than is usual. Most explanations of somatic hypervigilance implicate altered information processing, but strong empirical data are lacking. Attention and working memory are critical for information processing and we aimed to evaluate brain activity during attention/working memory tasks in people with and without somatic hypervigilance.

Methods: Data from 173 people with somatic hypervigilance and 173 controls matched for age, gender, handedness and years of education, were analysed. Event-related potential (ERP) data, extracted from the continuous electroencephalograph recordings obtained during performance of the Auditory Oddball task, and the Two In A Row (TIAR) task, for N1, P2, N2 and P3 were used in the analysis. Between group differences for P3 amplitude and N2 amplitude and latency were assessed with two-tailed independent t-tests. Between group differences for N1 and P2 amplitude and latency were assessed using mixed, repeated measures ANOVAs with Group and Group*Site factors. Linear regression analysis investigated the relationship between anxiety and depression and any outcomes of significance.

Results: People with somatic hypervigilance showed smaller P3 amplitudes (Auditory Oddball task: $t(285) = 2.32$, 95% CI [3.48; 4.47], $p = .026$, $d = 0.27$ and Two-In-A-Row (TIAR) task: $t(334) = 2.23$, 95% CI [2.20; 3.95], $p = .021$, $d = 0.24$) than case-matched controls. N2 amplitude was also smaller in people with somatic hypervigilance (TIAR task: $t(318) = 2.58$, 95% CI [.33, 2.47], $p = .010$, $d = 0.29$) than case-matched controls. Neither depression nor anxiety was significantly associated with any outcome.

Conclusion: People with somatic hypervigilance demonstrated an event-related potential response to attention/working memory tasks that is consistent with altered information processing.

Abstract Word Count = 289.

Keywords (somatic hypervigilance, event-related potential, working memory, perceptual processing, Auditory Oddball task)

Acronyms used in the text

EEG = electroencephalograph(y), ERP = event-related potential, SSD = somatic symptom disorder, PTSD = posttraumatic stress disorder, Fz = midline frontal electrode position, based on the 10-20 system, Cz = midline central electrode position based on the 10-20 system, Pz = midline parietal electrode position based on the 10-20 system, Hz = hertz, ms = milliseconds, dB = decibels, N1 = peak of activity coincident with the response to a stimulus and measured between 80 and 170 ms after the stimulus is presented, N2 = peak of activity coincident with the response to a stimulus and measured between 180 to 420 ms after a stimulus is presented, P2 = peak of activity coincident with the response to a stimulus and measured between 140 and 270 ms after a stimulus is presented, P3 = peak of activity coincident with the response to a stimulus and measured between 300 and 600 ms after a stimulus is presented, BRID = Brain Resource International Database, SPHERE = Somatic and Psychological Health Report, DSM V = Diagnostic and statistical manual of Mental Disorders V, DASS = Depression Anxiety Stress Scales,

Introduction

Somatic hypervigilance refers to an unintentional and efficient cognitive process by which the sufferer becomes preoccupied by somatic stimuli that are perceived as threatening, at the expense of other concerns (Crombez, Van Damme, & Eccleston, 2005). It is primarily thought to facilitate avoidance and escape behaviour and is associated with activation of the fear system (Crombez, et al., 2005). The construct of somatic hypervigilance is helpful in the clinical assessment and conceptualisation of a spectrum of disorders that are captured by the Diagnostic and Statistical Manual of Mental Disorders – V (DSM – V) classification of somatic complaints (American Psychiatric Association, 2013) including somatoform disorder, Post-traumatic Stress Disorder (PTSD), fibromyalgia, and chronic widespread pain conditions (Rief & Martin, 2014). Because the healthcare impact associated with these disorders is substantial (Access Economics Pty Ltd, 2007; Andersen, Eplöv, Andersen, Hjorthøj, & Birket-Smith, 2013; Smith, Monson, & Ray, 1986), investigations into the mechanisms contributing to their development and maintenance are warranted.

Most models of somatic hypervigilance consider that altered information processing plays a major role in the development and maintenance of symptoms (Brown, 2004; Crombez, Eccleston, Baeyens, Lysens, & Eelen, 1998; Crombez, et al., 2005; Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013; Crombez, Viane, Eccleston, Devulder, & Goubert, 2013; Pennebaker, 1982; Phillips & Clauw, 2011; Rief & Barsky, 2005; Rief & Broadbent, 2007; Rief & Martin, 2014; Witthoft & Hiller, 2010).

We know that people diagnosed with somatoform disorder scan their body for somatic signals more often than healthy controls (Rief & Barsky, 2005). That is, somatic signals take on an importance or are considered salient in this group. Indeed, once the innocuous somatic signals have come to mind, it is thought that they draw further cognitive appraisal, and invoke an ongoing cycle of signal amplification, somatic hypervigilance, and misperception, altering perception in favour of the bodily input (Brown, 2004; Rief & Barsky, 2005). Perturbed processes of memory and perceptual evaluation

are also thought to play a role, whereby the misperceived bodily signals generate a new multimodal representation of the body (Brown, 2004). In the current study, we were interested in whether people who report the clinical feature of somatic hypervigilance demonstrate altered information processing.

We explored information processing by evaluating aspects of cognitive function in people with somatic hypervigilance using two attention/working memory paradigms. Working memory is a critical component of information processing and is inextricably associated with the processes of attention (Baddeley, 2003; 2007, p. 67; Knudsen, 2007). For clarity, we consider attention to be the allocation of processing resources to currently relevant internal or external stimuli. In order to respond adaptively to the environment (both internal and external), one must select the information that is most relevant to them at that point in time. Signals that are relevant and/or important and/or novel (salient) are evaluated within the context of a current neural representation of bodily state. The most important signal (the one with the most relevance) competes for working memory resources and an adaptive response is generated (Desimone & Duncan, 1995; Egeth & Yantis, 1997). For example, imagine that you picked up a plate of food that was much hotter than you thought it to be, but because the plate is a treasured heirloom you adapt your first behavioural choice to drop it, and instead find the nearest place to set it down. People with somatic hypervigilance place importance on somatic signals and we are interested in the extent to which a novel signal will compete with the somatic signals for the resources of working memory. The extent to which resources are allocated to a task can be inferred from the timing and magnitude of cortical activity during the task.

The timing and magnitude of cortical activity can be captured and characterised from early to late stage of working memory processing using event-related potentials (ERPs) (Reinvang, 1999). Of

particular interest in tasks of attention/working memory is P3, a large, positive peak that occurs 300 to 600 milliseconds after stimulus onset. P3 is thought to be determined by the cognitive state of the person, more so than the sensory dimensions of the stimulus itself, and is considered a correlate of the interface between perception and attention (Johnson, Allana, Medlin, & Karl, 2013; Reinvang, 1999).

In keeping with recent guidelines for electroencephalography (EEG) (Keil, et al., 2014) we distinguished two variants of the P3 family by latency windows. The latency windows are different to account for the difference in actual ERP response waveforms between the two tasks and to maximise the sensitivity to real effects. A current understanding suggests that P3 reflects the cortical activity associated with the information processing cascade that occurs when memory and attention mechanisms are engaged and is sensitive to manipulation of memory load and task duration (Johnson, Allana, Medlin, Harris, & Karl, 2013; Pinal, Zurrón, & Díaz, 2014; Polich, 2007). The first, P3b, is elicited in the context of detecting a target stimulus during a standard Auditory Oddball task. P3b is understood to reflect the allocation of resources when information is maintained in working memory (Nathan, 2012; Polich, 2007, p. 161). Typically, P3b latency and amplitude is measured at the central parietal (Pz) electrode and is thought to reflect neural speed and use of cognitive resources, respectively (van Dinteren, Arns, Jongsma, & Kessels, 2014). Auditory Oddball P3b is considered the standard (Reinvang, 1999), robust (Duncan, et al., 2009) neuropsychological measure of P3b.

A second variant of P3, which we have labelled P3wm on the basis of two prior studies (Galletly, McFarlane, & Clark, 2008; Veltmeyer, McFarlane, Moores, Bryant, & Gordon, 2009), is elicited in the context of the Two In A Row (TIAR) task. P3wm is thought to reflect the processes that occur when information is maintained and updated in working memory. The amplitude of P3 in this context has been shown to differentiate people with PTSD and schizophrenia from controls (Galletly, et al., 2008;

Johnson, Allana, Medlin, & Karl, 2013; Veltmeyer, et al., 2009), and we were interested in whether people with somatic hypervigilance, often associated with PTSD, also produced an altered performance on this task. P3wm is typically measured at central parietal sites and a higher amplitude reflects the resources allocated to task performance (Saliasi, Geerligs, Lorist, & Maurits, 2013).

N2 is the secondary component of interest, because it too is thought to be determined by endogenous factors, such as cognitive set, and is considered to represent our ability to discriminate between stimuli (Näätänen & Gaillard, 1983; Reinvang, 1999). Typically, for both the auditory oddball and a visual paradigm such as the TIAR task, rare targets elicit a larger N2 over the parietal scalp and the latency of N2 covaries with reaction time (Folstein & Van Petten, 2008; Pinal, et al., 2014). Increased latency and amplitude of N2 in post-traumatic stress disorder (PTSD) has been linked to a decreased ability to discriminate between target and non-target stimuli (Galletly, et al., 2008). We were interested in whether this feature is also affected in people with somatic hypervigilance.

A positive deflection between 150 and 200 ms, P2, is a ubiquitous feature of an auditory evoked potential (Crowley & Colrain, 2004). The latency and amplitude of this component varies with features of the stimulus, such as stimulus intensity and stimulus pitch, but the functional significance of P2 remains poorly understood (Crowley & Colrain, 2004). N1, a negative deflection between 80 and 150 ms after stimulus presentation is thought to represent orientation of attention for the purpose of perceptual discrimination (Ohoyama, et al., 2012). The features of the stimulus such as a sudden change in stimulus character are thought to influence N1 latency and amplitude.

Behavioural measures of the task are also important as they are thought to provide information about a general style of response. For example, how often correct responses are missed or whether

there is a higher or lower rate of false positives. They also highlight differences in speed/accuracy trade-offs (Veldhuijzen, et al., 2006). Similarly, a construct that is closely related to somatic hypervigilance is anxiety sensitivity (Crombez, et al., 2005; Wong, et al., 2014). Because people with anxiety disorders such as PTSD and panic disorder have shown cognitive deficits (Galletly, et al., 2008; Wise, McFarlane, Clark, & Battersby, 2009), it is necessary to obtain clinically useful and valid measures of depression and anxiety in this cohort.

Our primary hypothesis was that people with somatic hypervigilance will demonstrate an ERP response profile to attention/working memory tasks (Auditory Oddball and TIAR) that is consistent with altered information processing. Specifically, we expected less activity during perceptual evaluation (smaller P3b and P3wm amplitude) in people with somatic hypervigilance than in healthy matched controls. We predicted that, at the interface between perception and attention, people with somatic hypervigilance may be using cortical resources for maintenance of the threatening body signals, leaving fewer for new perceptual evaluation, especially if the stimulus appears task-irrelevant (Kahneman, 1973; Wickens, 1981). We also expected that, because of a preoccupation with evaluating the threatening body signals, people with somatic hypervigilance would use more resources to discriminate between stimuli, and be slower to disengage resources, and make more total errors, relative to matched controls. That is, we expected a greater N2 amplitude and latency, and increased total errors in those with somatic hypervigilance than in matched controls. In keeping with earlier research, and to cover the window of information processing from stimulus presentation to decision making, we also assessed latencies and amplitudes at N1 and P2 for these tasks of attention/working memory.

Methods

Participants

Participants' data were obtained from the Brain Resource International Database (BRID <http://www.brainresource.com>). The BRID stores information about the brain in health and disease that has been collected in a standardised manner, using identical protocols, equipment, computer hardware, and software across laboratories located in Adelaide, Capetown, Durban, London, Melbourne, New York, Nijmegen, Pretoria, Rhode Island, Sydney, Tweed Heads, Wits and Union City. Test-retest and inter-laboratory reliability has been shown to be high (Clark, et al., 2006; Paul, et al., 2007; Williams, Simms, Clark, & Paul, 2005). The BRID makes the processed data available to the BRAINnet (www.BRAINnet.net) for scientific investigation. For clarity, descriptions of the BRID protocol will be in present tense and descriptions of the secondary analysis of data will be in past tense.

Participants for BRID are recruited in a number of ways; notices in school newsletters, media interview appeals, word of mouth and the use of advertising flyers on notice boards and a gratuity is offered for participation. Every participant provides informed consent and is assigned an eight digit identification number, which is linked to the database and establishes anonymity. All participants are fluent English speakers. Prior to laboratory attendance for testing, all participants complete between 17 and 27 web-based questionnaires encompassing questions relating to demography, lifestyle habits, and psychological symptoms. Participants are requested to avoid alcohol for 12 hours, and nicotine and caffeine for 2 hours prior to testing.

Of primary concern to this study were descriptive data including participants' age, gender, years of education, handedness, ethnicity, current use of psychoactive prescription medications, current smoking, and use of marijuana and alcohol. Somatic symptoms as measured by the Somatic and Psychological Health Report - 12 (SPHERE-12) Questionnaire (Hickie, et al., 2001), and Depression,

Anxiety and Stress scores from the Depression Anxiety Stress Scales – 21 (DASS - 21) were of prime importance. Processed data from behavioural and neurophysiological measures of neuropsychological performance were also important. Hereafter, 'participant' refers to the full data set obtained from a particular individual and stored in the BRID.

One hundred and seventy three participants were case-matched with healthy controls on four variables thought to influence attention/working memory performance: handedness, age, years of education, and gender (total n = 346). The somatic hypervigilance group consisted of participants who scored ≥ 3 out of 12 on the physical symptoms and fatigue (SOMA) scale of the SPHERE-12 Questionnaire, which is a sensitive identifier of people who are preoccupied by somatic symptoms (Hickie, et al., 2001 see details of this questionnaire under 'Demographic and Clinical Measures').

The matched controls (n =173) were included if they scored < 3 on the SOMA scale. All participants reported no pre-existing traumatic brain injury, major mental health, medical or neurological disorders. No participant was diagnosed with a psychiatric or psychological disorder. All participants had normal hearing, vision and dexterity, and were over 18 years of age.

Ethics

Ethics approval for secondary analysis of the data was granted by the Human Research Ethics committee at the University of South Australia. The research proposal was accepted without revision by scientific members of BRAINnet Foundation, who have a transparent process of approval of data use via peer consensus review.

Attention/ Working Memory Tasks

Auditory Oddball task protocol

Participants are asked to relax and to keep looking at a dot in the centre of the computer screen, while they are presented with a series of high and low pitched tones and asked to respond by button press to an infrequent high tone (1000Hz; target tone). The task instructions are standardised and request participants to press the response buttons with the index finger of each hand as fast and as accurately as possible whenever they hear the high-pitched tone. The target tone occurs as 15 % of the stimuli, the other 85 % of the stimuli consist of low-pitched non-target tones (500Hz). Target and non-target tones are presented in a quasi-random order with the constraint that no two target tones may be presented consecutively. Each tone is presented at 75 dB for 50 ms with a one second inter-stimulus interval. A total of 340 stimuli are presented and the task takes six minutes. Decibel levels are calibrated across sites using a sound decibel meter.

TIAR task protocol

A series of letters from a set (B, C, D and G) are presented one at a time on a computer screen in a quasi-random order. Participants are asked, using standardised task instructions, to identify when a letter appeared for the second time in a row (target stimulus). Participants indicate the target letter by a button press, and the speed and accuracy of the response are stressed to be equally important. In order to correctly distinguish target from non-target stimuli, participants must constantly update the information held within working memory, that is, keep a running track of the letters that are presented. Each letter is presented for 200 ms, with an inter-stimulus interval of 2.5 s. A total of 125 stimuli are presented of which 20 are target letters.

Standardised Electroencephalography Protocol

Electroencephalography testing is part of an overall laboratory procedure that takes place in a light and sound-attenuated room in which participants are seated comfortably, in front of a computer,

fitted with headphones and electroencephalograph (EEG) electrodes (Gordon, Cooper, Rennie, Hermens, & Williams, 2005). A Neuroscan 'QuickCap' collects the output from 26 electrodes positioned according to the 10-20 International system (Jasper, 1958), and sampled at a rate of 500Hz. Electrode impedance is kept at < 5 kOhms. An electrode on the forehead acts as ground and reference electrodes (A1 and A2) are placed on the earlobes. The 26 sites are: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, O2. The psychophysiological tests are completed in an identical manner by all participants. The task instructions are pre-recorded and delivered via headphones in a standardised manner.

ERP Data Extraction

ERP data are baseline corrected, the -300 to 0 ms prestimulus period is averaged and subtracted from the ERP signal for each channel. Data are extracted from the continuous EEG recordings obtained during performance of the Auditory Oddball task and the TIAR task and processed by BRID internal software. Recordings are signal-averaged at each electrode site in relation to each stimulus of interest: for the Auditory Oddball task, the stimuli of interest were the target tones; for the TIAR task, the stimuli of interest were the non-target stimuli, which reflect the process of working memory updating when a non-repeated letter becomes a new target. Prior to the averaging process, each single-trial waveform is filtered at 25 Hz with a Tukey or cosine taper to 35 Hz; no signal is passed above this frequency. An automated algorithm that is similar to the Gratton method (Gratton, Coles, & Donchin, 1983) is passed over the continuous data to correct for eye-blink artefacts. Three methods are used to reject ERP data for artefact: 1. Threshold based artefact rejection using an automated detector to identify any epoch that exceeds 100 μ V on at least 3 channels and thus mark the analysis as bad; 2. ERP specific rejection using cut off scores within which 99% of the epochs will fall and 3. Manual data rejection when the data are visually validated for artefacts by an expert technician and individual channels or the entire data may be marked as

bad. For method 2, measurements of the maximum, minimum, mean, range and average distance from the mean of ERPs are performed and channels that fall outside the following criteria are removed (measurements are in μV): maximum ($-6 < \text{maximum} < 70$), minimum ($-70 < \text{minimum} < 6$), mean ($-30 < \text{mean} < 30$), range (maximum – minimum < 110), average distance ($2 < \text{average distance} < 25$). The algorithm is deemed 98 % accurate and has been validated by experienced scorers (Gordon, et al., 2005; Haig, Gordon, Rogers, & Anderson, 1995).

The planned comparisons of the waveform peaks of amplitude for P3b (Auditory Oddball task), P3wm (TIAR task), and amplitude and latency for N2 (Auditory Oddball task and TIAR task) were determined at the midline site Pz. For the waveform peaks of amplitude and latency for N1, and P2, the three midline electrode sites: Fz (frontal), Cz (central) and Pz (parietal) were used. All electrode sites were selected for consistency with the existing literature (Galletly, et al., 2008; Gordon, Kraiuhin, Meares, & Howson, 1986; James, et al., 1987; Johnson, Allana, Medlin, Harris, et al., 2013; Nakao, Barsky, Nishikitani, Yano, & Murata, 2007). Following previous standard literature (Clark, Orr, Wright, & Weber, 1998), predetermined latency windows were used to determine the component peak, in this case for Auditory Oddball target stimuli: N1 (80 – 140 ms), P2 (140 – 270 ms), N2 (180 – 320 ms) and P3b (270 – 550 ms). For TIAR non-target stimuli the latencies were: N1 (80-170ms), P2 (100 – 250), N2 (180-420ms ms) and P3wm (280-550 ms). The latency windows are different to account for the difference in actual ERP response waveforms between the two tasks.

Behavioural Measures

The reported behavioural measures for the Auditory Oddball task and the TIAR task are speed (average reaction time for correct responses) and accuracy (number of false positives, number of false negatives and total number of errors).

Demographic and Clinical Measures:

The Somatic and Psychological Health Report (SPHERE - 12) Questionnaire

The SPHERE - 12 is a self-report screening tool for the classification of somatisation and psychological distress (anxiety and depression) in primary care (Hickie, et al., 2001). It comprises two, six item scales: 1. A SOMA scale for self-assessment of distressing, physical symptoms and fatigue; 2. A PSYCH scale for self-assessment of psychological health. The items are scored on a severity scale of 0-2, and ratings concern symptoms experienced 'over the past few weeks'. The SPHERE - 12 was designed for use in general practice as a tool for early detection of somatic hypervigilance and mental health disorders (Clarke & McKenzie, 2002; McFarlane, McKenzie, Van Hooff, & Browne, 2008). Cut-off scores for determining case-ness have been derived and validated in a cohort of 48,682 primary care patients (Hickie, et al., 2001). In this study, we used the score on the SOMA scale alone to group participants. In all cases their score on the PSYCH scale was disregarded because we used the scores from the DASS – 21 to investigate any relationship between anxiety and depression and outcomes of significance. Unlike the SPHERE – 12, the DASS is a quantitative measure and provides a richer source of information. High internal consistency and test-retest reliability has been demonstrated for the SPHERE – 12 (Hickie, et al., 2001).

The Depression Anxiety Stress Scales – 21 (DASS-21)

The core symptoms of depression, anxiety and stress were assessed using the DASS – 21. This scale has been shown have good reliability and validity (Henry & Crawford, 2005) particularly when used to compare groups of participants (Parkitny, et al., 2012). The DASS-21 comprises three distinct, yet correlated scales of seven questions each. Each item is scored on a four point severity rating scale (0 - 3) which reflects how much each statement applied to respondents over the past week. A total score for each scale is achieved by summing the respondent's scores to the seven statements.

Statistical analysis

Data Cleaning

Prior to statistical analysis, all data were inspected for the presence of missing values, errors, and outliers and to investigate whether the data met the assumptions for parametric analysis. Data normality was assessed using the Shapiro-Wilk statistic and visual inspection of the probability plots. Any ERP and behavioural data that were > 3 standard deviations from the mean were replaced with the group mean plus or minus three standard deviations (Leonowicz, Karvanen, & Shishkin, 2005). No demographic data were altered. The Huynh-Feldt correction factor for degrees of freedom (Huynh & Feldt, 1976) was used in analyses where the assumption of sphericity was violated and any violations are reported in the results. Bonferroni correction factor was used to control for Type I errors in all *post-hoc* tests. Effect sizes were calculated using partial eta squared (η_p^2) or Cohen's *d*, as appropriate (Field, 2009).

For a statistical power of 0.8 to detect a small to medium effect size (Cohen's $d = 0.4$), using an alpha of 0.05, for independent samples two-tailed t-test with a significance set at $\alpha = 0.05$, we needed 100 participants in each group. For a statistical power of 0.8 to detect a small effect size ($\eta_p^2 = 0.01$), using 0.05 alpha, for 2 x 3 mixed, repeated-measures ANOVAs we needed a total of 162 participants (Cohen, 1998). Analyses were undertaken using SPSS (SPSS version 21, IBM).

ERP Measures

Presuming the data were normally distributed, between-group differences for P3b and P3wm amplitude and N2 amplitude and latency (Auditory Oddball task and TIAR task) were assessed using four independent samples, two-tailed t-tests. If the data were not normally distributed or did not

satisfy the assumptions of parametric tests, the equivalent non-parametric tests were used.

Between-group differences for N1 and P2 amplitude and latency were assessed using 2 x 3 mixed repeated measures ANOVAs with Group (somatic hypervigilance versus controls) and Site (Fz, Cz and Pz) factors. Separate ANOVAs were conducted for the amplitude and latency of each component (i.e., four analyses). *Post-hoc* tests were conducted if any significant between-group effects relevant to the study aims were found. When there was a significant main effect of Group, a multiple linear regression analysis investigated the within group influence of depression and anxiety.

Behavioural Measures

Presuming the data were normally distributed, between group differences for average reaction time (ART), false positives (impulsivity), false negatives, and total errors were assessed for both the Auditory Oddball and TIAR tasks using eight independent samples, two-tailed t-tests. If the data were not normally distributed or did not satisfy the assumptions of parametric tests, the equivalent non-parametric tests were used.

Demographic and Clinical Measures

Age was analysed using an independent, two-tailed t-test. When random or systemic missing data caused unequal group sizes for any comparisons, between group differences for categorical variables (handedness, years of education and gender) were analysed using a X^2 test, and age was re-analysed using an independent, two-tailed t-test. Presuming the data were normally distributed, between group differences for the scales scores for the DASS – 21 were analysed using three independent samples, two-tailed t-tests. If the data were not normally distributed or did not satisfy the assumptions of parametric tests, the equivalent non-parametric tests were used.

Results

Data Cleaning and Matching

The electrophysiological and behavioural data met the assumptions for parametric analysis. Between group differences calculated for the DASS – 21 data scores used untransformed scores and the Mann Whitney U test. The average percentage of data replaced per variable was 3.83 %.

Demographics

Data were analysed for 173 people from either group. Age was not different between groups (mean (SD); Somatic hypervigilance group = 36.42 (16.86), Control group = 35.89 (17.27); $t(344) = -0.29$, 95 % CI [3.08, 24.58], $p = 0.78$). Table 1 shows the frequencies for handedness, gender, years of education and ethnicity. The largest ethnic group were those participants who reported their ethnic origins as European. Table 2 shows current use patterns between the groups for psychoactive prescription medication, smoking, marijuana and alcohol use; there were no clear differences between groups on these variables.

INSERT TABLE 1 ABOUT HERE.

INSERT TABLE 2 ABOUT HERE.

DASS –21

The somatic hypervigilance group scored higher on all three DASS – 21 scales than the control group ($p < 0.001$, see Table 3 for descriptive statistics).

INSERT TABLE 3 ABOUT HERE.

ERP findings

Descriptive and inferential statistics for ERP amplitude analyses for the somatic hypervigilance group and case-matched controls are shown in Figure 1 (Auditory Oddball task).

INSERT FIGURE 1 ABOUT HERE.

Auditory Oddball task t-test for P3b Amplitude

P3b amplitude was smaller in the somatic hypervigilance group than the control group ($t(285) = 2.32$, 95 % CI [3.48; 4.47], $p = 0.026$, $d = 0.27$). A multiple linear regression test showed neither depression nor anxiety were significantly associated with the outcome (see Table 4 for results of the multiple linear regression analyses for each significant outcome).

TIAR Task t-test for P3wm Amplitude

Descriptive and inferential statistics for ERP amplitude analyses for the somatic hypervigilance group and case-matched controls are shown in Figure 2 (TIAR task).

INSERT FIGURE 2 ABOUT HERE

P3wm amplitude was smaller in the somatic hypervigilance group than the control group ($t(334) = 2.23$, 95 % CI [2.20; 3.95], $p = 0.021$, $d = 0.24$). A multiple linear regression test showed neither depression nor anxiety were significantly associated with the outcome.

Auditory Oddball task N2 Amplitude and Latency

The groups were not different on N2 amplitude ($t(276) = 1.06$, 95 % CI [-0.51, 1.71], $p = 0.14$), or latency ($t(277) = -1.79$, 95 % CI [-15.14, 0.69], $p = 0.073$).

TIAR task N2 Amplitude and Latency

N2 amplitude was smaller in the somatic hypervigilance group than it was in the control group ($t(318) = 2.58$, 95 % CI [0.33, 2.47], $p = 0.010$, $d = 0.29$). Latency was not different between groups ($t(319) = 0.158$, 95 % CI [-8.22, 9.65], $p = 0.437$). A multiple linear regression test showed neither depression nor anxiety were significantly associated with N2 amplitude.

Auditory Oddball task N1 and P2

There was no Group effect, nor a Group*Site interaction for amplitude or latency of N1 or P2.

TIAR Task N1 and P2

There was no Group effect, nor a Group*Site interaction for amplitude or latency for N1 or P2.

INSERT TABLE 4 ABOUT HERE

Behavioural outcomes

Descriptive and inferential statistics for somatic hypervigilance and control groups for behavioural outcomes are presented in Table 5.

Auditory Oddball task

The groups were not different on ART, number of false positives (i.e. impulsivity), numbers of false negatives or total errors (i.e stimulus identification) for the Auditory Oddball task.

TIAR task

The groups were not different on ART, number of false positives (i.e. impulsivity), number of false negatives or total errors (i.e. stimulus identification) for the TIAR task behavioural outcomes.

INSERT TABLE 5 ABOUT HERE.

Discussion

Our primary hypothesis, that people with somatic hypervigilance will demonstrate an ERP response profile to attention/working memory tasks (Auditory Oddball and TIAR) that is consistent with altered information processing, was supported. Our case matched sample of people with somatic hypervigilance demonstrated significantly smaller P3b and P3wm amplitudes than the control group. We found no evidence to support our hypothesis of a larger amplitude or longer latency at N2, or a greater number of total errors in people with somatic hypervigilance. Conversely, we found reduced N2 amplitude on the TIAR task in people with somatic hypervigilance than in case-matched controls. We did not find any evidence to support between-group differences in processing at N1 or P2, for latency or amplitude, or for any behavioural outcome measures. We found no effect of depression or anxiety on any outcome measure of significance.

ERP findings

P3b and P3wm amplitude

That we found lower P3b amplitude and P3wm amplitude in the somatic hypervigilance group suggests that people with somatic hypervigilance have impairments in both the maintenance and the updating of working memory. . This is important because intact working memory is critical for many activities of daily living, goal- directed behaviour, and is essential for information processing and responding adaptively to novel situations (Baddeley, 2007; Hofmann, Schmeichel, & Baddeley, 2012). Indeed, impairments in working memory have been shown to contribute to much of the disability in disorders such as schizophrenia, where successful pharmacological treatments have shown only a modest effect on improving the cognitive symptoms of the disorder (Green, 1996; Keefe, Bilder, Davis, Harvey, & Palmer, 2007). Would it be surprising to find that working memory

impairments, not as yet routinely assessed or managed in people with somatic hypervigilance, might account for some of the disability associated with their conditions?

The size of the P3 amplitude has been shown to be sensitive to the attentional resources engaged in task performance during a dual task paradigm (Polich, 2007) and we interpret the smaller P3 amplitude to reflect that people with somatic hypervigilance used fewer resources for updating the percept and maintaining it, than the case-matched controls did. In healthy control samples, the more a primary task increases cognitive demands, the greater the decrease in P3 amplitude (Kramer, Wickens, & Donchin, 1985). Although we cannot be sure what task-unrelated cognitive processing people with somatic hypervigilance were engaged in during task performance, various theoretical models would suggest vigilant cognitive appraisal of incoming bodily signals might be a consideration (Nakao, et al., 2007; Rief & Broadbent, 2007; Rief, Hiller, & Margraf, 1998; Rief & Martin, 2014).

P3 is thought to represent the information processing cascade that occurs when memory and attention processes are engaged (Pinal, et al., 2014; Polich, 2007). A framework within which to consider the functional components of attention (Knudsen, 2007) suggests that a smaller P3 amplitude might also reflect a lack of stimulus salience. Salient stimuli, for example, those that are important or novel and hence stand out from other potential input, are evaluated within the context of dynamic neural representations that encode factors such as past experience, current internal state, long term memory, and any relevant environmental information (Desimone & Duncan, 1995; Egeth & Yantis, 1997). The stimulus with the highest overall signal strength will compete for control of working memory function. Concurrently, top down modulation of attentional focus and working memory control is influenced by motivational goals and other factors, such as priming of

information. In this way, the processes of attention and working memory form a feedback loop that directs effective, adaptive behavioural responses to suit immediate needs (Knudsen, 2007). It is plausible to suggest that the stimuli used in these paradigms were not the signals of highest immediate strength for people with somatic hypervigilance, and hence attracted the use of fewer resources.

A recent review showed that people with major depressive disorder demonstrated a diminished P3b (Nathan, 2012). Reduced P3b has also been found in a variety of anxiety disorders including panic disorder (Wise, et al., 2009) and PTSD (Johnson, Allana, Medlin, & Karl, 2013). Although the somatic hypervigilance group had higher levels of depression and anxiety than the control group, we did not find evidence to support an association between the levels of depression or anxiety and either P3b or P3wm in people with somatic hypervigilance. It is conceivable that because people with a psychological or psychiatric diagnosis were excluded, the resultant levels of depression and anxiety associated with somatic hypervigilance were not high enough to exert any effect on the neurophysiological outcomes.

TIAR task N2 amplitude

We predicted a larger N2 amplitude and longer N2 latency in the somatic hypervigilance group on the grounds that greater use of resources would be required to discriminate between stimuli in the event that a disability to disengage resources from distressing somatic signals led to a delayed, but greater use of resources. However, we instead found no delay, but a smaller N2 amplitude in people with somatic hypervigilance than in controls. One interpretation of these findings is that maintenance of contextual information (i.e. the constant body scanning and the upkeep of a new multimodal representation of body image) is prioritised over the discrimination of non-relevant

stimuli, as suggested by influential models of somatic hypervigilance (Brown, 2004; Rief & Broadbent, 2007; Witthoft & Hiller, 2010). In the present context, task-related stimuli might be accorded lower priority to disorder-related somatic symptoms. Also relevant here is evidence from research into those with chronic pain who show deficits in working memory (Berryman, et al., 2013) and executive function (Berryman, et al., 2014). In that group, the saliency of one's current concerns is thought to drive the frequency of task-unrelated intrusions, such as bodily signals (Crombez, Van Ryckeghem, et al., 2013), and to disrupt stimulus discrimination. People with chronic pain demonstrate clear diversion of attention towards low intensity, noxious distractors, when asked to respond to an auditory stimulus at the same time (Crombez, et al., 1998). Furthermore, people with chronic pain demonstrate more difficulty disengaging attention from the noxious stimuli (Van Damme, Crombez, & Eccleston, 2002). These effects have been generalised to signals of threat (Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004) and corroborate findings from people with PTSD, who have diminished ability to disengage from threat scanning and are known to be hypervigilant (Daniels, et al., 2010).

N1 and P2 amplitude and latency

N1 and P2 characteristics are determined by the physical properties of the stimulus (Reinvang, 1999) and the nature of the interaction between the stimulus presentation and the participant (Boutros, et al., 2000). For these components a larger amplitude is thought to reflect an exaggerated response to afferent input (James, Gordon, Kraiuhin, Howson, & Meares, 1990). Contrary to an earlier study that examined auditory evoked potentials and found a larger N1 amplitude to both target and non-target oddball stimuli (Gordon, et al., 1986) in people demonstrating somatic hypervigilance than in controls, we found no alterations at N1 in people with somatic hypervigilance. To date, and in keeping with our findings, no studies have found abnormalities at P2 in people with somatic hypervigilance. This suggests that the phenomenon of somatic hypervigilance is more likely to be

associated with top down (cortical) processing rather than amplification of bottom up signals. This is consistent with the current neuroplastic model of chronic pain that places high explanatory value on the cortical changes that accompany the disorder and its phenomena (Apkarian, Baliki, & Geha, 2009). The contrasting results from our study and the previous one may relate to the sample size and homogeneity (current study: n = at least 165 per group, homogenous inclusion criteria using the SPHERE – 12, and case-matched exactly for age, gender, and handedness and years for education; previous study: n = 10 per group, diagnostic inclusion criteria for the somatisation disorder group that required a minimum of 25 symptoms per person and only matched on gender and within 5 years of age). Nonetheless our results should clearly be replicated before whole-hearted endorsement of the findings.

Behavioural outcomes

In order to look for strategic trade-offs between speed and accuracy, behavioural measures remain a useful adjunct to neurophysiological measures. That we did not find any evidence for between group differences suggests people with somatic hypervigilance are no slower (ART), no more impulsive (for example increased false positives), nor less accurate (for example overall errors) in identifying the stimulus in the presented paradigms than case-matched controls. A mismatch between neurophysiological and behavioural outcome measures as reported in this study, has been also been reported in the existing fibromyalgia literature (Glass, et al., 2011; Mercado, et al., 2013), albeit during tasks of inhibition. Here the task was thought to be too simple to tax the remaining cortical resources beyond their capacity to perform the task accurately and with speed. Future studies that vary the cognitive load are needed in order to interrogate the mismatch.

Implications for treatment and future directions

Our research suggests that somatic hypervigilance is associated with altered information processing, including alterations in attention/working memory processes. The clinical applicability of the findings remains limited, because although there is much conjecture about the processes that may be reflected by the changes, no precise target for treatment intervention has been established. One may contend on the strength of the key findings, that the clinical assessment of working memory (and restorative intervention) in conditions that are likely to present with somatic hypervigilance, such as people with chronic pain, or fibromyalgia, is warranted. Progress in this direction, however, awaits the establishment of clinically useful, standardised working memory testing protocols and evidence based interventions. In order to disentangle the contributions to information processing, future study designs also need to account for at once the many factors that may influence these processes, including competing demands, emotional factors, mood and motivation (Wiech & Tracey, 2013). More complex analyses such as mathematical and causal modelling is needed to account for these factors.

Strengths and Limitations

A clear strength of the current work is the sample – a relatively homogenous sample that was at least 4.3 times larger than any previous work and case-matched participants to controls on four variables. Analysis protocol was set a priori and we applied conservative statistics. Interpretation of the results should of course consider potential limitations. Although our design controlled for age, education, handedness and gender, we were not able to control for other factors thought to modulate P3, most notably IQ, medication and sleep quality (Polich & Kok, 1995). Our study involved secondary analysis of previously collected data, which, although data were collected using standard protocols and our study was approved after peer review by a team incorporating the investigators who collected the primary data, brings with it a risk of subtle differences in methods although it eliminates the possibility of double entry data. Because the number of artefacts may differ greatly

between groups or conceivably between laboratories it is important to report the percentage of trials rejected due to artefact. Although a robust protocol for handling artefacts is stipulated by BRID protocol, the percentage of trials rejected due to artefact were not available from the database, and thus our interpretation of the results was limited. Future study designs might seek to recruit a medication-naïve sample from the community, implement a pre-experiment wash-out period, or cluster participants according to the type and dose of medications. Such approaches would offer new and important information, but they would also result in a less pragmatic evaluation of the sample. Additionally, future studies and inter-study comparisons would benefit from the standardisation of collection methods for sleep-related variables.

Conclusion

People with somatic hypervigilance demonstrate an ERP response profile to attention/working memory tasks that is consistent with perturbed information processing. The abnormal profile is not due to age, gender, handedness, education, or levels of depression or anxiety. Despite the perturbation in information processing, people with somatic hypervigilance perform normally on behavioural outcomes of the tasks.

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