bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Altered cognitive processing of tactile stimuli in patients with Complex Regional Pain Syndrome (CRPS)

Authors and Affiliations

Anoop Kuttikat [1], Valdas Noreika [2], Srivas Chennu [3], Nicholas Shenker [1], Tristan Bekinschtein [2], Christopher A. Brown [4]

[1] Department of Rheumatology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

[2] Department of Psychology, University of Cambridge, Cambridge, United Kingdom; Medical Research Council, Cognition and Brain Sciences Unit, Cambridge, United Kingdom.

[3] School of Computing, University of Kent, Chatham Maritime, United Kingdom. Department of Clinical Neurosciences, University of Cambridge, United Kingdom.

[4] Department of Psychological Sciences, Faculty of Psychology, Health and Society, University of Liverpool, Liverpool, United Kingdom. CamPAIN group, Department of Anaesthesia, University of Cambridge, Cambridge, United Kingdom.

Corresponding author

Christopher Brown

Email: cab79@liverpool.ac.uk

Telephone: 0151 794 2174

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Disclosures

The research was supported by funding from Cambridge Arthritis Research Endeavour (CARE). The study was sponsored by Cambridge University Hospitals NHS Foundation Trust and supported by its Rheumatology department. The authors report no conflicts of interest.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Abstract

Chronic pain in CRPS has been linked to tactile misperceptions and deficits in somatotopic representation of the affected limb. Here, we identify altered cognitive processing of tactile stimuli in CRPS patients that we propose marks heterogeneity in tactile decision-making mechanisms. In a case-control design, we compared middle and late-latency somatosensory-evoked potentials (SEPs) in response to pseudo-randomised mechanical stimulation of the digits of both hands (including CRPS-affected and non-affected sides) between 13 CRPS patients and 13 matched healthy controls. During a task to discriminate the digit simulated, patients (compared to controls) had significantly lower accuracy and slowed response times but with high between-subject variability. At middle latencies (124-132ms), tactile processing in patients relative to controls showed decrements in superior parietal lobe and precuneus (that were independent of task demands) but enhanced activity in superior frontal lobe (that were task-dependent). At late latencies, patients showed an augmented P300-like response under task demands that localised to supplementary motor area (SMA). Source activity in SMA correlated with slowed response times, while its scalp representation intriguingly correlated with better functioning of the affected limb, suggesting a compensatory mechanism. We present evidence of altered but highly variable cognitive processing (124 - 268ms latency) in response to mechanical tactile stimuli in patients with CRPS compared to healthy controls. Such mid-to-late latency responses could potentially provide convenient and robust biomarkers of abnormal perceptual decision-making mechanisms in CRPS to aid in clinical detection and treatment. Future research should investigate the clinical utility of these putative markers of tactile decision-making mechanisms in CRPS.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Keywords

Chronic pain; CRPS; neuroplasticity; biomarkers; EEG; cognitive; tactile.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Introduction

Complex Regional Pain Syndrome (CRPS) is an unexplained chronic, debilitating pain condition that is characterized by disproportionate pain, swelling, vasomotor, sudomotor, trophic and motor changes. The clinical heterogeneity of the condition points to mechanistic heterogeneity (Marinus et al., 2011) and there is a clear and unmet need to better characterise patients in terms of underlying mechanisms to aid early detection and targeted treatment [1]. Observations of tactile misperceptions in patients with CRPS have prompted investigation of somatosensory neuroplasticity as a putative mechanism in CRPS pain [2]. However, there is a range of responses to tactile misperception tasks across samples of CRPS patients. For example, in one such test requiring patients to identify the digit touched without corresponding visual information, just less than half of CRPS patients perform poorly on the affected hand [3]. Despite this variable performance across patients, such metrics (which include lower accuracy in discrimination but also longer response times) improve classification of CRPS patients from patients with limb fracture, even if the patients suffer from lower-limb CRPS and are tested on their hands [4]. This lack of spatial specificity suggests central mechanisms may influence performance decrements and supports further investigation of such mechanisms.

Decrements in tactile spatial discrimination in CRPS patients [5] have been associated with neuroplasticity involving shrinkage of the somatosensory cortical homunculus [5], which physical treatments can plausibly remedy [5–10]. Shrinkage of Penfield's homunculus would be consistent with reduced tactile perceptual resolution and an increased rate of tactile misperceptions. Investigations of these phenomena have used the high temporal resolution

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

of MEG and EEG, focussing on early latency (<100ms) cortical tactile responses arising from somatotopic cortical representations. However, there is a lack of research investigating later "cognitive" stages of tactile processing. We hypothesised that some aspects of deficits in tactile discrimination in patients with CPRS could be related to aberrant perceptual decision-making mechanisms at late latencies. Identifying CRPS patients who are characterised by these mechanisms may have implications for treatment.

Important aspects of cognitive processing of sensory stimuli are indexed by the P300, a robust late-latency component occurring ~200–400 ms post-stimulus. A rationale for investigating the P300 is its potential as a robust biomarker of cognitive dysfunction. For example, EEG research in other clinical contexts has found that P300 marks cognitive dysfunction in chronic headache [11], chronic lower back pain [12], phantom limb pain [13], schizophrenia [14], disorders of consciousness [15] and dementia [16]. The P300 is thought to reflect cognitive updating processes that are sensitive to task demands (providing a marker of attentional resource allocation). Thus P300 responses typically correlate with stimulus-response times [17], providing a potential marker of perceptual decision-making efficiency. P300 is also responsive to stimulus probability, with larger responses to rare stimuli thought to reflect bottom-up prediction error signals [18,19].

Considering these attributes, a number of competing predictions can be envisaged regarding how late-latency tactile processing could be affected in CRPS. Firstly, if there is a loss of somatotopic resolution as previous work suggests, an increase in task difficulty and therefore cognitive load would be expected on tasks requiring tactile spatial discrimination,

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

thereby predicting augmented cognitive processing (particularly in frontal cortical areas) in CRPS patients. A second possibility is that cognitive processing is altered regardless of task demands owing to deficits in spatial representations of the body, which involve hierarchically lower representations in somatosensory cortex and parietal association areas. A third possibility is reduced novelty-related cognitive processing in frontal areas in response to stimuli occurring at rare spatial locations, which would occur if those novel locations could not be as efficiently discriminated in CRPS patients. Here, we sought evidence for these different possibilities by measuring SEPs elicited on stimulation of randomised digit locations across both hands in CRPS patients and matched healthy controls.

Materials and Methods

Study design and rationale

This was an experimental case-control study conducted in the EEG lab in the Herchel Smith Building for Brain and Mind Sciences, University of Cambridge, UK between March 2013 and July 2013. Ethical approval for the research was obtained by the East of England - Cambridge South ethics committee (reference number 12/EE/0305). The study was designed to detect group differences (between CRPS patients and healthy controls, HC) in mid-to-late latency (>100ms) tactile processing. In Experiment 1, participants performed a digit discrimination task to induce cognitive load and SEPs were investigated as a potential explanation for

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

decrements in task performance. At the same time, the three middle digits on each hand were stimulated rarely compared to the outer digits in order to assess the effects of spatial probability. Experiment 2 had no task demands and had equiprobable digit stimulation, providing data on group differences independent of cognitive load. SEPs were recorded using high density (92-channel) EEG, making comparisons between groups, between CRPS-affected and unaffected sides of the body, and between digit types (high vs. low probability).

Sample size

At the stage of study design and conduct, tools were not available for powering EEG studies for group contrasts using contemporary statistical methods for EEG as used in this report. Reporting of sample size calculations in the EEG/ERP literature is estimated to be extremely uncommon for this and a number of other likely reasons [20]. The aim was therefore to recruit as many as possible/practical with the available resources bearing in mind that many published EEG studies of CRPS report on around 10 subjects. Our aim was to recruit 20 patients, half of whom we expected (based on past literature [3]) to show signs of digit misperception, and an equal number of healthy control participants.

Participants

Potential Complex Regional Pain Syndrome (CRPS) participants were identified from the CRPS UK registry and were approached for taking part in the study. The total number of potentially eligible CRPS patients contacted (who lived locally) was 30; 25 of these were

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

confirmed eligible, of which 16 patients were able to be recruited before the recruitment period of the study ended. All patients were diagnosed with unilateral upper or lower limb CRPS according to modified Budapest Research Criteria [21]. The inclusion criteria were kept as broad as possible, including upper and lower limb-affected patients on the left or the right side. Although the study tests involved digit stimulation and discrimination on the hand only, previous work [4] has found that the location of CRPS symptoms (namely, upper vs. lower limb) does not significantly affect performance in digit discrimination. Also recruited were 13 age-and-sex frequency-matched healthy (pain-free) volunteers. Healthy volunteers were recruited by advertising the study using posters in Addenbrooke's Hospital, Cambridge, UK. All participants signed an informed consent form prior to taking part.

Data from 3 patients were excluded from the study analysis: one did not complete the study, and in the other two patients, data quality was extremely poor due to extreme movement artefact that could not be corrected or removed. This results in 13 patients (11 females, mean age=46.8 years). Of these patients, five had left arm, three had right arm and five had left leg affected respectively. The mean disease duration was 5.3 years (range 1-14). Demographic and medical details of the participants are shown in Tables 1 and 2. All participants were right handed, did not have any current or previous diagnosis of peripheral neuropathy, stroke, transient ischemic attack, multiple sclerosis, malignancy or seizure. The participants were required to refrain from consuming alcohol or smoking tobacco for 24 hours and caffeine for 12 hours prior to the study.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Study Procedures

During the study visit, CRPS patients (but not healthy controls) were further characterised by using five questionnaires assessing pain severity, physical function, depersonalisation and mood: Brief Pain Inventory [22] – pain numerical rating scales only, Upper Extremity Functional Index [23], Lower Extremity Functional Index [24], Neglect-like Symptom Questionnaire [25], Hospital Anxiety and Depression Scale [26].

For the EEG experiments, participants were seated in a comfortable chair in an acoustically and electrically-shielded room. The room was air-conditioned and temperature of the room kept constant within the limits of 18 - 22°C. Adjacent to the testing room was a connected investigator room, where participants could be observed and heard using a headphone and video monitoring system. Participants were fitted with the EGI electrolyte cap with 128 channels (although only 92 channels were analysed – see pre-processing procedures). The correct size of the cap for the individual participant was determined by measuring the head circumference. The cap was soaked in a solution of water and potassium hydrochloride for 10 minutes before fitting on the participant. The salt-water solution was pipetted into sponges of electrodes necessary to achieve good impedances (below 100 kΩ). Participants were instructed to keep their eyes closed and head still as much as possible during testing to minimise eye blink, muscle and movement artifacts. Participants were provided with soft ear plugs to block out any extraneous auditory input so that they could focus on tactile stimulation. Soft tactile stimuli were delivered to the tips of the digits of both hands using custom-made hand-boxes (one for each hand) that were calibrated to deliver non-painful stimuli with the same force. The participants were advised to report immediately if the

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

sensation was uncomfortable or painful. The fingertips were also checked after each session to check for any redness of the skin. With this device and the EEG, two experiments were conducted as follows.

Experiment 1

The main aim of Experiment 1 was to record (i) behavioural accuracy and response time for identification of each digit stimulated, (ii) SEPs related to task-relevant and spatially probabilistic tactile processing. The experiment consisted of 80 trials per block and four blocks per hand. The participants were given a small break of few minutes between each block. Only one hand was tested in a block and the order of the hand stimulation was randomised across blocks. Each trial lasted a maximum of 3 seconds, or terminated sooner depending on the speed of participant responses. The 80 trials per block were split into 30 each for thumb (digit 1) and little finger (digit 5) and the remaining 20 split between the remaining three fingers (Figure 1a). This resulted in a significantly higher probability of digits 1 and 5 (37.5% of the time for each, or 75% in total) being stimulated compared to digits 2, 3 and 4 (8.3% each, or 25% in total). Over the 4 blocks, 80 trials were presented for the total of the middle three digits (D2-D4) and 120 for each of the little finger and thumb; this provided more than enough data for robust measurement of the P300 potential, thought to require a minimum of 36 clean trials [27].

For each block, participants were instructed to place one hand on the corresponding hand-box at a time. The digit positions on the hand-box were numbered consecutively from one to five starting with thumb (i.e.; thumb=1, index finger=2, middle finger =3, ring finger=4

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

and little finger=5) – see Figure 1a. Each time the subject received a stimulus (with duration of 0.05s) on a digit they responded by verbalising the number corresponding to that digit. A microphone attached to the EMG leads on the polygraph input box was used to capture the participant's response time, measured as the time from the delivery of the stimulus to the start of the voice deflection on the EMG lead recording. Following verbal responses, the experimenter manually triggered the next stimulus by a key-press.

Experiment 2

The main aim of the Experiment 2 was to study group differences in SEPs in the absence of cognitive task demands. In this experiment, participants were instructed to sit relaxed with eyes closed and head still and without responding to stimuli. 100 stimuli were delivered per digit of each hand (Figure 1a), split into two blocks per hand with the block order randomised. The digit order of stimulation was randomised within each block. Stimuli were delivered at 1 Hz: the stimulus duration was 0.05s with an inter-stimulus interval of 0.95s. There was a 10s break after every 50 stimuli.

EEG data acquisition and pre-processing

During the experiment, 128-channel high-density EEG was recorded (but only 92 channels analysed) using the Net Amps 300 amplifier (Electrical Geodesics Inc., Oregon, USA). Due to the use of naturalistic touch stimuli with relatively long stimulus durations (compared to electrical stimuli, for example), early components (e.g. <100ms) were expected to be difficult to detect, and as our main interest was long-latency components, the sampling rate

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

was set at 250 Hz. The vertex electrode (Cz) was used as a reference. Data from 92 channels over the scalp surface (at locations shown in supplementary Figure 1) were retained for further analysis, with channels excluded on the neck, cheeks and forehead, which mostly contributed movement-related noise than signal in patients.

EEG data pre-processing was performed using EEGLAB version 13.1.1 [28]. Continuous data were initially high-pass filtered at 0.5 Hz and low pass filtered at 30Hz. After filtering, data were segmented into epochs including from 200ms preceding the stimulus to 800ms post-stimulus. Data containing excessive eye movement or muscular artefact were rejected by a quasi-automated procedure: noisy channels and epochs were identified by calculating their normalised variance and then manually rejected or retained by visual confirmation. Independent component analysis (ICA) based on the Infomax ICA algorithm [29] was run on the clean data excluding bad channels using the 'runica' function in EEGLAB. ICA components were visually inspected and bad components rejected. Bad channels previously identified by visual inspection were then replaced by spherical spline interpolation of neighbouring electrodes. Data were then re-referenced to the average of 92 channels. ERPs were calculated for each subject, experiment and digit type by averaging epochs.

Definition of conditions for behavioural and ERP analyses

For all analyses, we considered three factors in the analysis: Digit Type, Side affected (by CRPS), and Group (CPRS, HC). Some explanation of these factors is provided here. The 'Side' factor levels were defined as affected and unaffected based on CRPS clinical assessment (Table 2). 4 patients were affected on the right side (2 upper limb, 2 lower limb) and 9

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

patients on the left side (5 upper limb, 4 lower limb). Due to the small sample size, we could not consider left-affected and right-affected CRPS patients, or upper and lower limb-affected patients, as separate groups. For the HC group to act as an adequate control, because no limbs were affected, we chose to consider four of the healthy participants' right arm data and the remainder of the healthy participants' left arm data as the 'affected' condition for the HC group, to match the left/right ratio of side affected in the CRPS group. The four HCs whose right-arm data was designated as 'affected' were chosen as those recruited in the same order as those CRPS patients who right arms were affected (i.e. participants 1, 4, 7 and 8 – Table 2). To be explicit, the term 'affected' in the HC group denotes a control condition for the CRPS 'affected' condition, and does not imply the presence of CRPS symptoms in the HC group.

In Experiment 1 only, for the 'Digit Type' factor, trials from stimulation of digits D2, D3 and D4 on each hand were considered as a single level which we subsequently label as 'D2-D4', and analysed alongside D1 and D5 to result in three digit types in total. Aside from their spatial location, D2-D4 digit trials were considerably more rare (low probability) than D1 or D5 trials (see Experiment 1 procedure). For Experiment 2, on the other hand, all digits were considered as separate levels (5 in total).

Behavioural Data Analysis

Prior to testing our main hypothesis regarding cognitive cortical processing in CRPS, we sought to replicate and extend the results of previous work [3,4] that found reductions in accuracy and increases in response time in similar digit discrimination tasks in CRPS patients.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Specifically, we tested a number of hypotheses, namely (H1) that there would be a group difference in at least one of these metrics, (H2) in the CRPS group (compared to the HC group), at last one of these metrics would indicate worse performance on the affected vs. the unaffected side of the body, indicating some somatotopic specificity, (H3) there would be slower response times to stimulation of rarer spatial locations (D2-D4) than more frequent locations (D1 and D5) due to the cognitive cost of switching attention to rarer locations, (H4) this cognitive switching cost would be less evident in the CRPS group compared to the HC group if they are less accurate at discriminating between digits in the first place.

Behavioural data from Experiment 1 were analysed using IBM SPSS (Statistical Package for Social Sciences) software version 21 [30]. Data for accuracy and response times were not normally distributed, especially in the CRPS group. Hence, non-parametric tests were performed to investigate overall group differences averaged over all conditions (Mann-Whitney U test), and to investigate within-subject condition effects in each group separately (Wilcoxon signed rank tests). Effect sizes are reported for non-parametric statistics using the formula $Z/\sqrt{N}$, where Z is the z-value output of the test and N is the number of samples in the test. This provides an effect size equivalent to the Pearson's coefficient r, commonly interpreted as a small, medium and large effect with values of 0.1, 0.3 and 0.5 respectively.

EEG Sensor-Level Analysis

SPM12 (www.fil.ion.ucl.ac.uk/spm) was used for subsequent EEG analysis steps [31]. A "sensor-space" analysis was conducted (the standard approach implemented in SPM [32]).

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

This analysis deals with the multiple comparisons problem (in this case, statistical inference over many peri-stimulus time points and many electrodes) in a way that does not require narrowing down the search space by making assumptions as to the precise timing or topographic location of physiologically important events. More precisely, random field theory (RFT) is used to make inferences over space and time while adjusting P-values in a way that takes into account the non-independence of neighbouring sensors and time-points. Applying to smooth data, the RFT adjustment is more sensitive than a Bonferroni correction. Hence, after data conversion from EEGLAB to SPM format, for each participant, experiment and digit, SPM EEG sensor data were transformed to 3-D Scalp [x, y] × Time [z] images and smoothed in the spatial dimension to 12mm full-width half-maximum (FWHM). For all analyses, the temporal window-of-interest was 100 – 400ms.

Analyses required direct comparisons between data derived from stimulation of CRPS-affected vs. CRPS-unaffected sides of the body. Due to the small sample size, we could not consider left-affected and right-affected CRPS patients as separate groups. Without further spatial transformation of the data, then, collapsing the data for “affected” and “unaffected” stimulation conditions across left and right-affected patients would have resulted in a mixture of left and right-hand stimulations respectively within each condition. As such, the identification of lateralised responses (e.g. the expected contralateral dominance for certain ERP components) would have proved problematic as both contralateral and ipsilateral data (from different patients) would have been mixed together within each condition. To resolve this problem, all sensor-space images representing cortical responses to right-hand stimulation were flipped on the x-axis. This resulted in images that represented (actual or

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

apparent) left-sided stimulation, such that all contralateral differences resulting from hand stimulation on affected vs. unaffected sides would appear in the right hemisphere of the sensor-space images rather than being dispersed between both hemispheres.

Statistical analysis was performed on the resulting images with correction for multiple comparisons using random field theory to take into account the smoothness of the data on the scalp (Kilner & Friston, 2010). To do this, a General Linear Model (GLM) was estimated at the group level consisting of the between-subject factors Subject and Group (CRPS, HC), and the within-subject factors Side (affected, unaffected) and Digit (D1, D2-D4, and D5). F-contrasts were then constructed. Three effects were relevant to our hypothesis: (1) the main effect of Group, to test whether there are overall differences in cognitive processing in patients with CRPS, (2) the interaction of Group*Side, to test whether cognitive processing differences in CRPS are specific to the affected side, (3) the interaction of Group*Digit Type (in Experiment 1 only), to test whether any group effects depend upon the spatial probability of stimulation. For Experiment 2, the GLM was estimated in the same way and the contrasts were the main effect of Group and the Group*Side interaction.

EEG Source-Level Analysis

Analysis at the source level was based on time windows defined from group differences on the sensor level. Canonical sensor locations were coregistered with the canonical head model in SPM. Lead field computation used a boundary element model (Phillips, Mattout, & Friston, 2007). The Bayesian source reconstruction method in SPM was used (Mattout,

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Phillips, Penny, Rugg, & Friston, 2006) with Multiple Spare Priors to estimate sources across the temporal window of interest (100 to 400 ms). Subsequently, source activity was averaged in each time window corresponding to the latency of significant effects of interest from the sensor-space analyses. Using F contrasts, significant differences were identified in source space and reported significant at a cluster-level significance of p (FWE) < 0.05 when considering statistical maps thresholded at $p < 0.001$.

Brain-Behavioural Correlations

Neural correlates of behavioural outcomes in the patient group (namely, the hypothesised lower accuracy and slower response times) were investigated in source space. Regions-of-interest were identified as those clusters in the parietal and frontal lobe showing significant Group effects in the SPM contrasts, and were extracted from the SPMs as eigenvariates. To reduce the number of comparisons being made, where bilateral group differences were evident, sources from both clusters were averaged together prior to correlation analysis. Correlations using Spearman's rank coefficient were conducted in the patient group only to understand behavioural variance within this group (also, accuracy scores in the control group were not variant enough to justify such analyses within the control group).

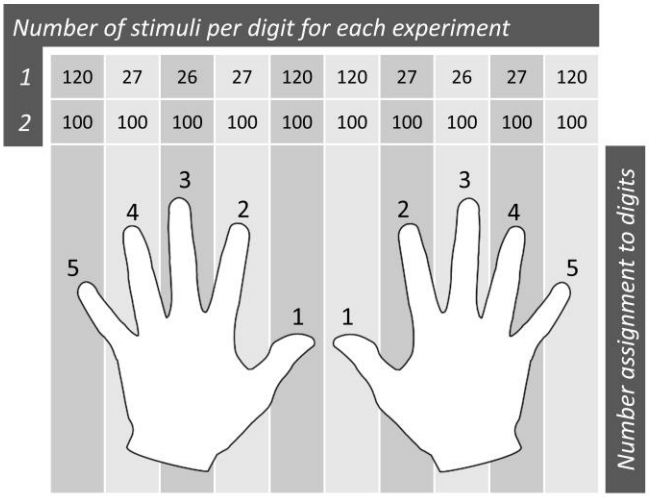
Secondary (exploratory) correlation analyses

As clinical data were collected using a number of questionnaires (clinical pain ratings, anxiety depression, limb functioning, neglect-like symptoms), we performed exploratory analyses to test for correlations between these clinical variables and digit discrimination

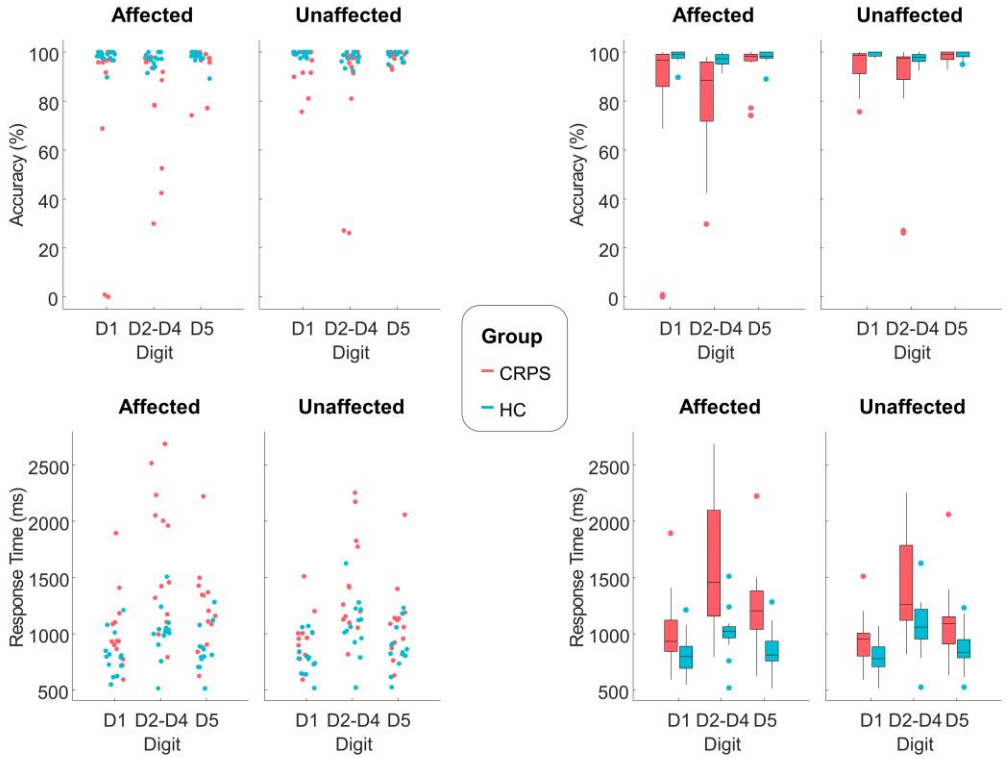
bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

task-related (behavioural and EEG) outcomes. As well as testing against EEG source activity, we also explored clinical variable relationships with sensor-space clusters. Finally, we explored relationships between sensor-space clusters in the EEG data across the different latencies, as well as source-space clusters across latencies.

A



B



bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Figure 1*: (A) The number of tactile stimuli delivered to each digit (randomised on each hand in turn) and the number assignment to each digit that the subject used to respond as to which digit was stimulated. (B) Behavioural results. Top: Accuracy data. Bottom: Response time data. Plots on the left (jittered dot plot) and right (box plot) are different representations of the same data.*

Results

Demographics

There were 13 patients with unilateral upper or lower limb CRPS of which 11 were females and two males. 10 had left sided CRPS and three had right sided CRPS. Five had left arm affected, three had right arm affected and five had left leg affected. There were 13 age and sex matched healthy volunteers. All subjects (patients & healthy) were right handed. The baseline details of the subjects are documented in Tables 1 and 2.

Table 1*: Participant characteristics*

Characteristics	**CRPS (n=13)**	**Healthy (n=13)**
Age in years **Mean (range)**	46.8 (30-63)	45.0 (28-63)
Female sex (%)	11 (84.6)	11 (84.6)
Right handed (%)	13 (100)	13 (100)

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Dyslexia (%)	0		0
Disease duration in years Mean (range)	5.3 (1-14)		Not applicable
Past Medical History	Depression/Anxiety	7 (53.8)	None
	Other psychiatric	**0**	
	IBS	0	
	Asthma/COPD	**6 (46.2)**	
	Migraines	2 (15.8)	
	Other medical	**8 (61.5)**	
Medications at the time of study (%)	Paracetamol	10 (76.9)	None
	NSAIDs	**4 (30.8)**	
	Weak opioids	5 (38.5)	
	Strong opioids	**2 (15.4)**	

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

	Anti-depressants	7 (53.8)	
	Anti-convulsants	**6 (46.2)**	
	Other medications	6 (46.2)	
Questionnaire data	**Brief Pain Inventory subscales:**		Not recorded
	- Maximum pain	7.1 (2.1)	
	- Least pain	5.1 (2.2)	
	- Average pain	6.0 (1.7)	
	Hospital Anxiety and Depression Scale:		
	- Anxiety	9.5 (5.9)	
	- Depression	8.0 (3.9)	
	Neglect-Like Symptoms Questionnaire	4.6 (0.9)	
	Upper/Lower Extremity Functional Index (scores for affected limb only):	58.5 (23.3)	

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

***Table 2**: Patient characteristics*

Patient Identifier	Age	Gen-der	Area affected	Disease duration (years)	Past Medical History	Medications
P1	34	F	Right leg	1	Raynaud's phenomenon	Amitriptyline, Pregabalin, Paracetamol, Tramadol
P2	59	F	Left leg	8	Osteoarthritis Migraine, Cervical spondylosis Uterine fibroids	Chondroitin, Glucosamine
P3	63	F	Left arm	8	none	Pregabalin, Paracetamol Tramadol, Lidocaine patch
P4	42	F	Right arm	5	Rotator cuff Tendinopathy	Ibuprofen, Paracetamol , Tramadol
P5	53	F	Left leg	14	Asthma, Hypertension, Vitamin D deficiency, Depression/Anxiety	Tiotropium, Amitriptyline Duloxetine, Ramipril, Bendroflumethiazide, Paracetamol, Simvastatin Tramadol, Adcal D3,QVAR GTN spray, Omeprazole

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

P6	30	F	Left leg	5	Depression	Amitriptyline, Oxynorm, Paracetamol, Fluoxetine, Carbemazepine, Oxycontin
P7	57	F	Right arm	3	Migraine, Spondylosis cervical Depression, Asthma, Anxiety Hypertension	Amitriptyline, Pregabalin MST continus, Ramipril, Lactulose, Mebeverine Diazepam, Fluoxetine Furosemide, Naratriptan Symbicort
P8	52	F	Right leg	4	Adhesive capsulitis, Asthma, Anxiety	Naproxen , Paracetamol
P9	50	F	Left arm	5	Asthma, Anxiety/Depression	Beclomethasone Salbutamol, Nortriptyline Paracetamol, Tramadol Fluoxetine
P10	59	M	Left leg	5	Anxiety	Amitriptyline
P11	29	M	Left arm	3	Adhesive capsulitis	Amitriptyline, Ibuprofen, Gabapentin, Adcal D3

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

P12	34	F	Left leg	3	Joint Hypermobility Raynaud's, Asthma, Anxiety, Depression	Symbicort, Naproxen Pregabalin, Paracetamol Adcal D3, Sertraline, Zopiclone
P13	43	F	Left hand	5	Asthma	Beclomethasone, Buprenorphine patch Gabapentin, Paracetamol, Imipramine, Omeprazole

Table 3*: Number of patients with CRPS in each body location*

	Left	**Right**
Hand/Arm	5	2
Leg	4	2

Behavioural Data

We hypothesised worse digit discrimination performance in the CRPS compared to the HC group in at least one of the metrics of accuracy and response time (RT). This hypothesis was supported. Accuracy in digit discrimination was lower on average for CRPS patients vs. healthy controls (HCs), but as shown in Figure 1b this was clearly driven by a small number

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

of CRPS patients. The remainder of the CRPS group's accuracy overlapped with that of the HCs, leading to a distribution of data strongly skewed towards high accuracy. Inferential statistics on the accuracy data provided a medium-to-large effect size in comparing the two groups (Table 4) with a *p* value of just over 0.01 (which remains significant after Bonferroni correction for the two tests – on accuracy and RT – used to address the hypothesis). For the RT data (Table 5 and Figure 1b), results were in a similar direction to the accuracy data but the group effect was stronger. In the CRPS group, while the distribution of the data was skewed towards lower RTs (Figure 1b), this did not appear to be strongly driven by such a small number of patients as for accuracy data. In addition, RTs showed overall greater variability in the CRPS group compared to the HC group. On average, RTs were longer in CRPS compared to HC participants with inferential statistics (Table 5) revealing a large effect size with strong statistical significance.

We further hypothesised that in the CRPS group, there would be worse performance (for at least one of the metrics) on the affected vs. the unaffected side of the body, indicating some somatotopic specificity In the CRPS group. As shown in Figure 1b, there was some indication of worse performance on the affected side compared to the unaffected side in CRPS patients. To address this hypothesis statistically, we looked at both the main effect of Side (pooling over both groups) and the interaction between Group and Side (a Group contrast on the subtracted Side data, i.e. unaffected minus affected side – Table 4). For accuracy data, there was a significant main effect of Side (remaining significant after Bonferroni correction for four tests) with a large effect size, but no significant interaction between Group and Side. Hence, there is little evidence for a Side effect on accuracy that is specific to

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

the CRPS group, possibly due to a bias in performance in the HC group favouring the dominant hand (the "affected" condition in healthy controls mostly included data from the non-dominant hand). Conversely, for RTs there was no significant effect of Side across the two groups pooled together and the effect size was small (Table 5), but there was a significant interaction effect of Group and Side with a large effect size. It is visible from Figure 1b that on average, RTs were longer on the affected side in the CRPS group, but not in the HC group. Hence, RTs appear to be more specifically affected than accuracy by the side of the body stimulated in CRPS patients.

A separate hypothesis was that RTs would be longer on digits stimulated more rarely, but that this effect would be less apparent in the CRPS group due to a loss of discrimination accuracy. This hypothesis was only partly substantiated. A visible delay of RTs is evident for both groups in Figure 1b on more rarely stimulated middle digits (D2-D4) compared to more frequently stimulated digits (D1 and D5). Indeed, using inferential statistics pooling over both groups, there was a very strong Digit Type effect (Table 5). However, there was a medium-sized effect on the interaction between Group and Digit Type in the opposite direction to that hypothesised, with the mean difference in RTs between rare and frequently stimulated digits being 473 (SD 308) for the CRPS group and 203 (SD 108) for the HC group. In other words, there is no evidence to support the hypothesis that there is less cognitive cost to stimulating rare (vs. frequent) digit locations in CRPS patients because they are less able to discriminate the location changes.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

There is also a suggestion from the boxplot of Figure 1b of lower accuracy on middle digits (D2-D4 condition), compared to D1 and D5, in the CRPS group. While this is not relevant to our hypothesis, for exploratory purposes, the statistics for the Digit Type effect and interaction between Group and Digit Type are also shown for the accuracy data in Table 4. In sum, accuracy was overall lower for rarer digit stimulations, but there was no evidence of this differing between groups.

***Table 4**: Non-parametric test statistics for accuracy*

Group / Group effect	***Condition / Condition effect***	***Z statistic***	***p***	***Effect size (Z/√N)***
CRPS < HC (N = 26)	**All conditions**	2.28	0.011*	0.44
	Side (unaffected - affected)	1.65	0.055	0.32
	Digit Type (rare - frequent)	1.65	0.055	0.32
CRPS & HC (N = 26)	**Side (affected < unaffected)**	2.65	0.004*	0.52
CRPS & HC (N = 26)	**Digit Type (rare - frequent)**	3.19	<0.001*	0.63

One-tailed uncorrected *p* values shown; * indicates significant after Bonferroni correction; & indicates pooled data, < or > indicates a statistical contrast, - indicates subtraction of meaned data.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

***Table 5**: Non-parametric test statistics for response time*

Group / Group effect	***Condition / Condition effect***	***Z statistic***	***p***	***Effect size (Z/√N)***
CRPS < HC (N = 26)	**All conditions**	2.54	0.005*	0.50
	Side (unaffected - affected)	2.85	0.002*	0.56
	Digit Type (rare - frequent)	2.33	0.010*	0.46
CRPS & HC (N = 26)	**Side (affected < unaffected)**	1.41	0.080	0.28
CRPS & HC (N = 26)	**Digit Type (rare < frequent)**	4.43	<0.001*	0.89

One-tailed uncorrected *p* values shown; * indicates significant after Bonferroni correction; & indicates pooled data, < or > indicates a statistical contrast, - indicates subtraction of meaned data.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

EEG Sensor-Space Data

SPM sensor-space analyses were conducted on spatially-transformed sensor data (see Methods) such that all contralateral responses appeared on the right side of the scalp topography. In Experiment 1, the main effect of Group revealed significantly higher amplitude responses in a contralateral cluster at 132ms (negative polarity) and a fronto-central cluster at 268ms (positive polarity) in the CRPS group compared to the HC group (Figures 2 and 3, and Table 6). The positive peak at 268ms is consistent in timing and topography with a P300 response. However, there were no main effects of Digit Type or Side at either the 132ms or the 268ms latency. The lack of a Digit Type effect is contrary to our prediction that the P300 amplitude would be modulated by spatial probability.

At 132ms, the Group differences appear visually to be larger for the affected side compared to the unaffected side (Figure 2B); however, this did not translate into a statistically significant interaction between Group*Side, nor was there an interaction of Group*Digit Type. On the other hand, it is visually clear that at 268ms (Figure 3b) there are only Group effects and no interactions between Group and either Side or Digit Type, as borne out by the lack of statistical evidence for such interactions here either.

In Experiment 2, the main effect of Group revealed a similar contralateral effect as Experiment 1 although slightly earlier at 124ms (Figure 4a). Again, mirroring the data from Experiment 1, there is the visual resemblance of a possibly larger Group effect for the affected side than for the unaffected side, and yet no statistically significant interaction effects were evident. There was no Group effect at around the latency of a P300 response,

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

but for comparison with Experiment 1 the data from Experiment 2 are plotted at 268ms (Figure 5).

Table 6: *Sensor-space results*

	Spatial coordinates X, Y	**Latency (ms)**	***F***	**k**	***p* FWE (cluster-level)**	***p* FWE (voxel-level)**
Experiment 1	0, 18	268	34.31	2100	0.002	<0.001
	60, -30	132	26.76	1322	0.014	0.003
Experiment 2	21, -25	124	24.23	903	0.022	0.011

Spatial coordinates are indicated by X (left to right) and Y (posterior to anterior). Statistics include variance explained by the full model (*F* ratio), the cluster extent (k: number of voxels) and its associated cluster-level *P*-value (FWE corrected), in addition to the smallest voxel-level *P*-value (FWE-corrected) within the cluster.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

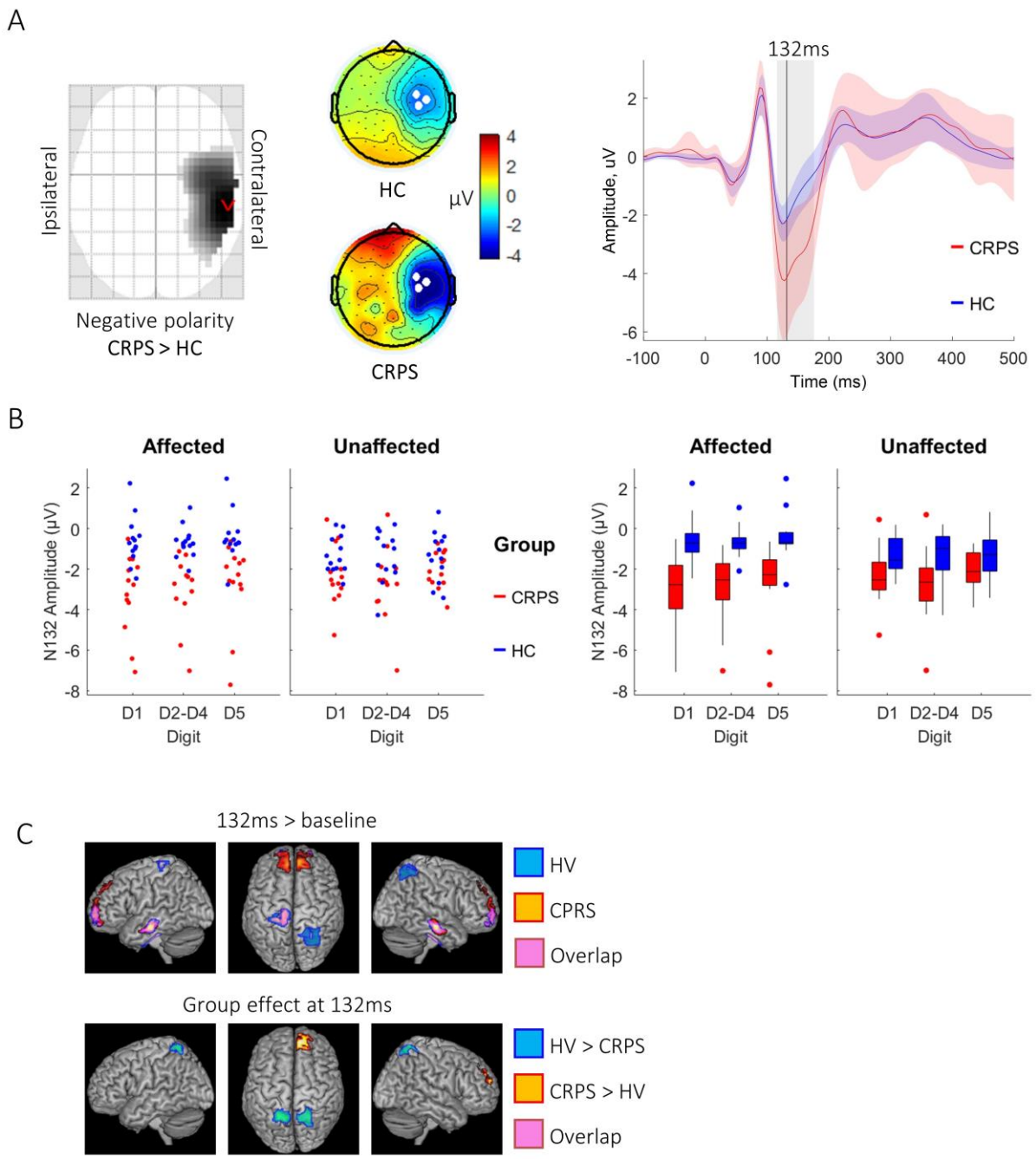


Figure 2: *Experiment 1 data at 132ms. A) Left: Statistical Parametric Map identifying greater negative polarity response at 132ms in the CRPS vs. HC group over contralateral temporal and parietal electrodes. Image is thresholded at p < 0.001 uncorrected. Middle: Grand-average topographic maps from each group; white filled circles show the three electrodes with the most negative amplitude at 132ms that were averaged to display the waveform.*

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Right: Waveforms with 95% confidence intervals showing the latency at 132ms (black line) and the temporal extent of the SPM sensor-space cluster (grey box). B) Two representations (jittered dot plot, left; box plot, right) of the activity in the significant sensor-space cluster for each group, side and digit type. C) Source-space results from the contrasts N132 activity vs. Baseline (top) and CRPS vs HC group (bottom) and their overlap (pink).

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

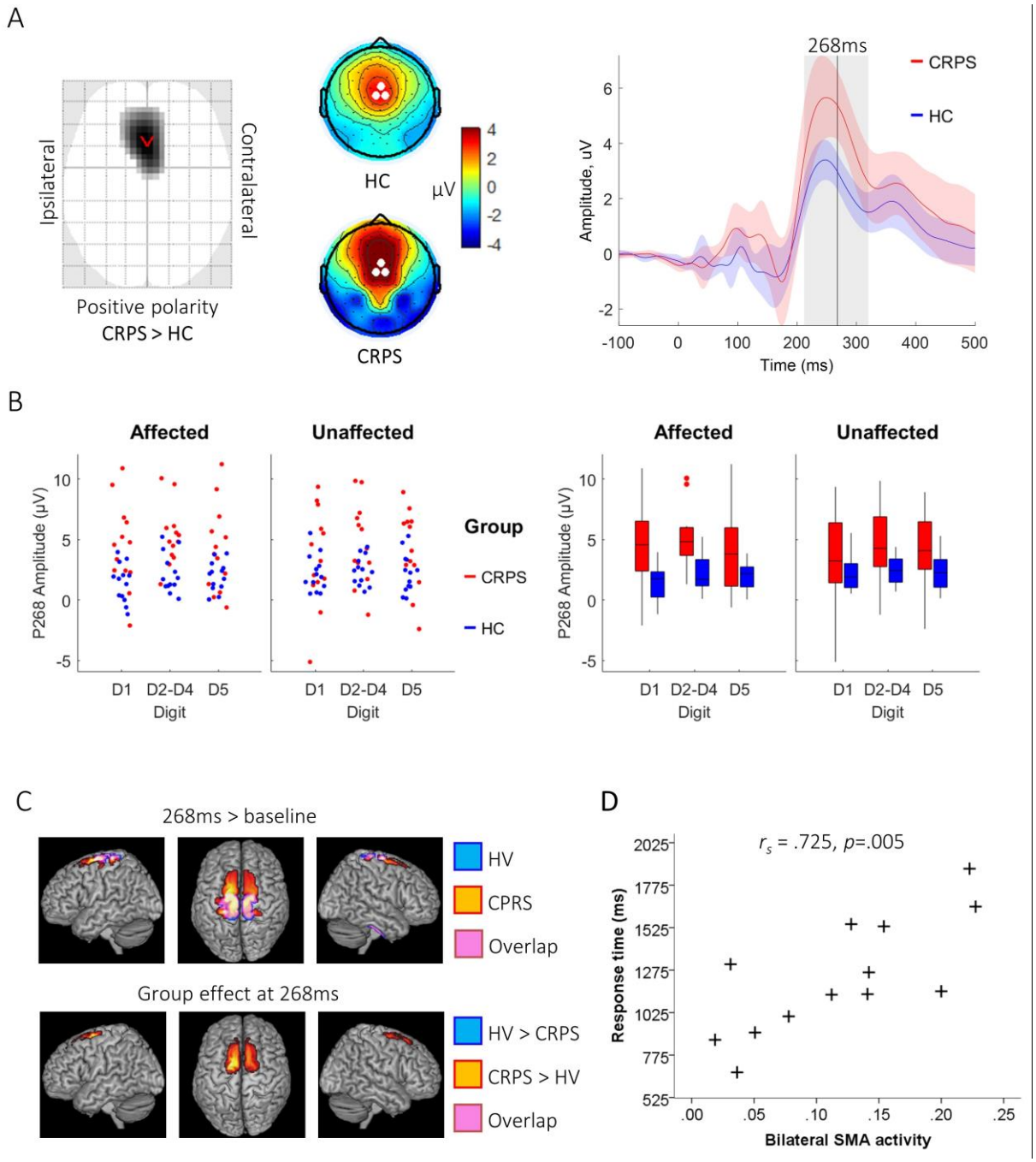


Figure 3: *Experiment 1 data at 268ms. A) Left: Statistical Parametric Map identifying greater positive polarity response at 268ms in the CRPS vs. HC group over frontocentral electrodes. Image is thresholded at p < 0.001 uncorrected. Middle: Grand-average topographic maps from each group; white filled circles show the three electrodes with the most positive amplitude at 268ms that were averaged to display the waveform. Right: Waveforms with 95% confidence intervals showing the latency at 268ms (black line) and the temporal extent*

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

of the SPM sensor-space cluster (grey box). B) Two representations (jittered dot plot, left; box plot, right) of the activity in the significant sensor-space cluster for each group, side and digit type. C) Source-space results from the contrasts P268 activity vs. Baseline (top) and CRPS vs HC group (bottom). D) Non-parametric correlation of activity in bilateral Supplementary Motor Area (SMA, cluster defined from the CRPS > HC group contrast) with digit discrimination response time.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

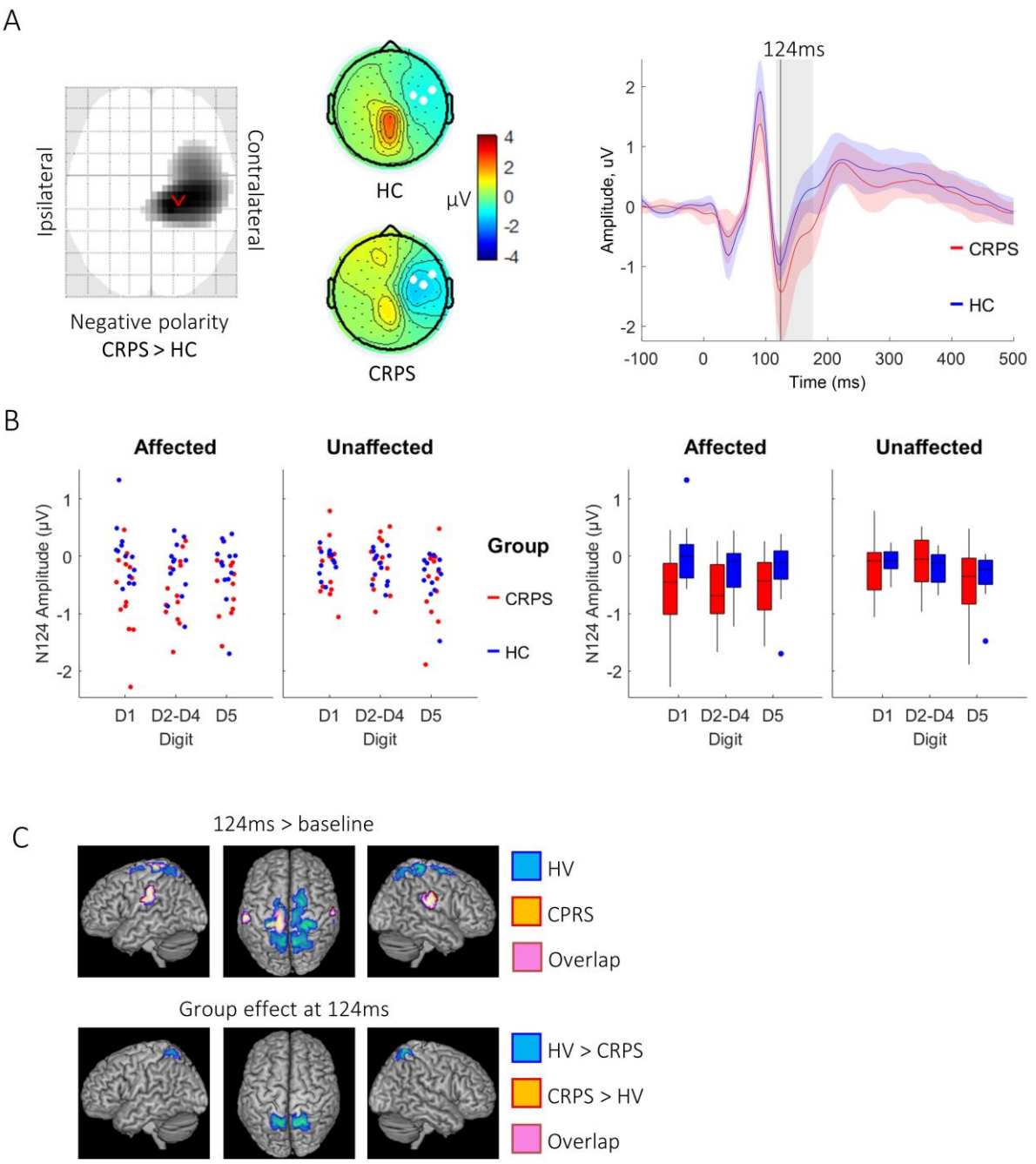


Figure 4: *Experiment 2 data at 124ms. A) Left: Statistical Parametric Map identifying greater negative polarity response at 124ms in the CRPS vs. HC group over contralateral temporal and parietal electrodes. Image is thresholded at p < 0.001 uncorrected. Middle: Grand-average topographic maps from each group; white filled circles show the three electrodes with the most negative amplitude at 124ms that were averaged to display the waveform. Right: Waveforms with 95% confidence intervals showing the latency at 124ms (black line)*

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

and the temporal extent of the SPM sensor-space cluster (grey box). B) Two representations (jittered dot plot, left; box plot, right) of the activity in the significant sensor-space cluster for each group, side and digit type. C) Source-space results from the contrasts N124 activity vs. Baseline (top) and CRPS vs HC group (bottom).

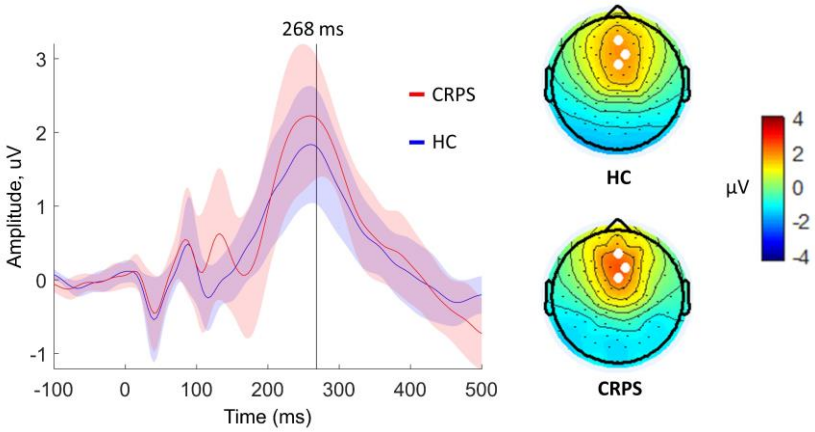


Figure 5: *Experiment 2 data at 268ms demonstrating a P300-like response but no group effects. Left: Waveforms with 95% confidence intervals showing the latency at 268ms (black line) at which the topographic maps are displayed. Right: Grand-average topographic maps from each group; white filled circles show the three electrodes with the most positive amplitude at 268ms that were averaged to create the waveform.*

EEG Source-Space Results

Sources of SEPs were estimated at latencies showing statistical significance in sensor-space. At each latency and for each group, contrasts are firstly reported for source activity (across all conditions) relative to pre-stimulus baseline as one-sided t-contrasts (supplementary Tables S1 and S2, and Figures 2c, 3c and 4c). Secondly, group effects are reported as two-sided F-contrasts (Table 7). To summarise the results in relation to the hypothesised group

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

differences, CRPS patients showed reduced activity in the precuneus and superior parietal lobe bilaterally in both Experiment 1 and Experiment 2 at middle latencies (132/124ms), suggesting a task-independent tactile processing deficit. On the other hand, greater activity was found in superior frontal areas in the CRPS group compared to the HC group in Experimental 1 (under task demands), which provides an explanation for the augmented responses found in the CRPS group in the analyses of sensor-space data. Specifically, middle latency responses were greater in a rostro-dorsal region of superior frontal lobe, while greater activity centred on the SMA at the later (268ms) latency.

To elaborate, in Experiment 1, sources of the SEP at 132ms (vs. baseline) that were common to both groups (Tables S1 and S2 and Figure 2c, top), included a sensorimotor cluster ipsilateral to the side of stimulation covering dorsal parietal regions of paracentral, precentral and postcentral cortex (an opposite, contralateral source did not reach statistical significance in either group). A further parietal source was only present in the HC group that included contralateral superior parietal lobe and precuneus. In the group contrast at 132ms (Table 7 and Figure 2c, bottom) this superior parietal / precuneus cluster was found to have a significantly larger activation in the HC group compared to the CRPS group, alongside an equivalent ipsilateral cluster. In the frontal lobe, there were common activations at 132ms beyond baseline in the most rostral portion of the superior frontal lobe bilaterally (Tables S1 and S2 and Figure 2c, top). However, in CRPS patients this activity extended to a more dorsal region bilaterally, and in the group contrast (Table 7 and Figure 2c, bottom) was found to be of significantly greater activity on the contralateral side in this rostro-dorsal region. This frontal activity likely explains the larger contralateral negativity in the CRPS group at 132ms

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

(Figure 2a). Other regions of activity at 132ms beyond baseline were shared by the two groups: posterior cingulate cortex and middle temporal lobe. Further clusters in bilateral medial temporal lobe regions (fusiform/parahippocampus) were evident in the HC group and not the CRPS group, but showed no differences in the group contrast.

In Experiment 1 at a latency of 268ms, the main sources of activity in both groups vs. baseline (Tables S1 and S2 and Figure 2c, top) were in an ipsilateral and a contralateral cluster covering dorsal regions of paracentral, precentral, postcentral gyri and supplementary motor area (SMA). In CRPS patients, these clusters extended more rostrally to include larger areas of SMA and the superior frontal lobe. The group contrast (Table 7 and Figure 3c, bottom) confirmed significantly larger bilateral SMA / superior frontal cortical activity in the CRPS group compared to the HC group, corresponding to the larger fronto-central negativity found in the CRPS group in sensor-space (Figure 3a). Further sources were evident that were unique to each group but not significantly different in the group contrast: superior parietal and posterior cingulate cortex in the CRPS group, and fusiform/parahippocampal gyrus in the HC group.

In Experiment 2, sources of activity at 124ms that were common to both groups (Tables S1 and S2 and Figure 4c, top) were bilateral clusters in ventral regions of postcentral gyrus, supramarginal gyrus and Rolandic operculum, commonly considered as secondary somatosensory association cortex, and an ipsilateral dorsal region of the paracentral and postcentral gyri. The HC group, however, showed considerably more widespread activity in superior parietal lobe and precuneus bilaterally, confirmed to be significantly greater than in

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

the CRPS group in the group contrast (Table 7 and Figure 4c, bottom). This finding is consistent with the group differences in topography of the SEP at 124ms (Figure 4a, middle) in which the HC group show a larger positivity at posterior midline electrodes, although this was not a statistically significant difference in the sensor-space analyses. Rather, as clear from Figure 4a, statistical significance was restricted to a larger contralateral negativity in CRPS patients. This latter group difference is not matched to an equivalent source-space group difference in contralateral cortex, but could be reasonably hypothesised to arise from activity in secondary somatosensory cortex whose activity was shared by both groups.

Table 7: *Source-space results for the contrast of CRPS group vs. HC group*

	Latency (ms)	**Region**	**Spatial MNI coordinates X, Y, Z**	**k**	**P FWE (cluster -level)**	**F**	**P FWE (peak-level)**
Experiment 1	132	Precuneus / Sup. Parietal (I)	-22, -54, 66	268	0.004	24.15	0.04
	132	Precuneus / Sup. Parietal (C)	22, -56, 64	293	0.003	21.19	0.14
	132	Medial Sup. Frontal (C)	8, 52, 34	189	0.02	22.26	0.09
	268	SMA / Sup. Frontal (I)	-16, 0 , 68	764	<0.001	57.83	<0.001
	268	SMA / Sup. Frontal (C)	10, 4, 68	592	<0.001	35.20	<0.001

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Experiment 2	124	Precuneus / Sup. Parietal (I)	14, -58, 66	469	<0.001	29.08	0.012
	124	Precuneus / Sup. Parietal (C)	-8, -56, 64	338	0.006	26.22	0.003

Spatial coordinates are indicated by X (left to right), Y (posterior to anterior) and Z (inferior to superior). Statistics include variance explained by the full model (*F* ratio), the cluster extent (k: number of voxels) and its associated cluster-level *P*-value (FWE corrected), in addition to voxel-level statistics including the minimum *P*-value (FWE-corrected) within the cluster.

Neural correlates of task performance

Temporal regions-of-interest from sensor-space topography maps (leftmost on Figures 2a, 3a and 4a) at 132ms and 268ms (Experiment 1) and 124ms (Experiment 2) were extracted for correlation analyses with behavioural data (accuracy and response time) in the patient group. No statistically significant correlations were found.

Regions-of-interest in the source data (clusters showing group differences in parietal and frontal areas) were also extracted for correlation analyses with behavioural data (accuracy and response time) in the patient group. Bilateral clusters were averaged together prior to analysis, resulting in a total of eight correlations (Table 8). After Bonferroni correction for multiple comparisons, a significant effect was found for response time - a positive correlation with source activity in SMA at 268ms during Experiment 1 (Figure 3d).

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Table 8: Source-behaviour correlation results

	Experiment 1			**Experiment 2**
	Precuneus, 132ms	Sup. frontal, 132ms	SMA, 268ms	Precuneus, 124ms
Accuracy	r_s = .033 p = .915	r_s = .418 p = .156	r_s = -.192 p = .529	r_s = -.484 p = .94
Response time	r_s = .099 p = .748	r_s = -.060 p = .845	r_s = *.725** p = .005	r_s = .412 p = .162

P values are reported uncorrected; for multiple comparisons a threshold of significance is applied of $p < 0.0063$. Significant values are denoted by an asterisk.

Exploratory correlation results

Supplementary tables S3 to S5 show the results of exploratory correlation analyses. Due to the large number of comparisons in the correlations of SEP data with clinical variables, only one relationship merits attention due to its strong correlation (r_s = .829, p = 0.0005) that survives multiple comparisons correction, namely the positive correlation between sensor-space cluster activity at 268ms in Experiment 1 with the lower/upper extremity function index, indicating that large P300-like responses predict higher levels of physical functioning of the affected limb in CRPS patients. Also of note is a correlation between the parietal and frontal sources showing group effects at 132ms in Experiment 1, which were correlated in both groups. Otherwise, sources were not correlated across latencies.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Discussion

The findings are consistent with our main hypothesis that cognitive processing during tactile perceptual decision-making, downstream of early-latency somatotopic mapping, is altered in patients with CRPS. Secondarily, consistent with previous reports [3,4], there was evidence of less accurate digit discrimination and longer response times in CRPS patients compared to controls, but a high degree of between-subject variability indicating heterogeneity in the mechanisms driving these performance indices. Interestingly, response times appear to provide a more robust behavioural marker of perceptual decision-making deficits in CRPS patients than measures of digit discrimination accuracy: Not only was the response time difference between groups a stronger effect, but it was also more evenly distributed across patients and more sensitive to stimulation on the affected vs. the unaffected side of the body. Furthermore, response times provided utility in characterising sources of augmented P300-like responses in SMA, positively correlating with longer response times in CRPS patients. Conversely, decrements in activation of precuneus and superior parietal lobe in patients with CRPS (compared to healthy controls) were not related to performance markers; further investigation is required as to the origin and functional consequences of these parietal lobe decrements.

A limitation of the present study was the small sample size, which can impact the robustness and generalisability of group comparisons. Furthermore, the variable nature of the behavioural and EEG outcomes suggests that future research should focus on exploring this variability in relation to clinical heterogeneity. While some aspects of clinical heterogeneity may be related to variable tactile processing, other aspects may not. For

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

example, previous reports found no difference in the prevalence of abnormal digit perceptions between upper and lower-limb affected CRPS patients [4]. Another example of heterogeneity is disease duration (which in the current study ranged from 1 year to 14 years); to date, there has been no systematic investigation of abnormal tactile perception of cortical processing in relation to this factor.

A further limitation is that the experiment failed to identify differential EEG responses to stimulation at more rare (8% probability) vs. less rare (37.5% probability) digit locations. It could be that the relative difference in rarity between conditions was not sufficient – 37.5% is still quite rare. On the other hand, response times were sensitive to the effect of rarity, and, counter to our predictions, CRPS patients were more sensitive to this effect rather than less. A plausible explanation is that longer response times on the middle three digits were affected by the additional spatial ambiguity arising from the fact that each of the middle digits (D2-D4) has two adjacent digits rather than just one for the outer digits (D1 and D5). CRPS patients may be more sensitive to this spatial ambiguity than controls. The experiment was therefore not well optimised to measure the effect of novelty-related responses as a potential marker of ineffective spatial discrimination in CRPS.

In the following, we discuss the results with reference to our two other predictions, that of augmented cognitive processing in patients specific to task demands, and altered task-independent processing related to spatial representations of the body.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Late-latency SEPs mark abnormal cognitive processing in CRPS

A key finding relating to our hypothesis was the larger amplitude positive polarity response at 268ms in CRPS patients compared to controls. The latency and scalp distribution of this effect is consistent with a P300 response; while the response was also observed in Experiment 2, it was substantially diminished (indicating sensitivity to task demands) and there was no group difference. Hence, this evidence supports the view that augmented task-related activity at 268ms in CRPS patients is due to the need for greater attentional resources to perform the task in this group.

However, attention is influenced by both endogenous (related to task demands) and exogenous (stimulus-driven) processes. While the task-specificity of the group effect on the P300 suggests a role for endogenous processes, some characteristics of the response also suggest a role for bottom-up deficits in CRPS patients. Specifically, endogenous and exogenous processes are reflected in two well-known sub-components of the P300 that have different latencies and scalp distributions: P3a ("novelty P3") is an earlier-latency fronto-central component that is sensitive to stimulus-driven processes related to infrequent stimuli, while the P3b ("classic P3") is a later-latency posterior-central component that reflects the degree of endogenous attention to the task when stimuli are repetitive [18,33]. There are three characteristics of our results that suggest the group difference at 268ms in the present study reflects differences in P3a-like stimulus-driven processing. Firstly, the early latency (for a P300) and fronto-central scalp distribution is reminiscent of a P3a. Secondly, the stimulus probabilities ranged from 8% to 37.5% depending on the digit, each of which can be considered spatially rare and therefore 'novel'.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Thirdly, previous studies of visual P3b-like components have identified that amplitudes are negatively related with RTs to the stimulus, possibly reflecting greater endogenous attention to the task [17]; this is opposite to our finding in CRPS patients when considering SMA sources of the 268ms, a finding more consistent with stimulus-driven processes interrupting and delaying decision-making and subsequent response to stimuli. Shorter RTs to visual targets have also previously been found to be preceded by greater *pre*-stimulus activation of SMA, thought to promote top-down vigilance towards expected stimuli [34]. In the present study, *post*-stimulus SMA activity predicted *longer* rather than shorter RTs, suggestive of stimulus-driven disruption of motor performance rather than top-down vigilance.

Interestingly, the magnitude of the P300 activity in CRPS patients predicted better limb functioning, suggesting it compensates to the disease rather than directly marking disease pathology, but we can only speculate about why this might be the case. While SMA is a premotor area that has an important role in the control of movements, it has also been implicated in broader perceptual and decision-making functions. Bilateral SMA (as well as, to a lesser extent, right precuneus) is particularly involved in maintenance of working memory required to discriminate between tactile stimuli separated by short delays [35–37], as well as in a subsequent decision-making phase [38]. Therefore, it may be that higher-level cognitive processing of lower-level deficits in spatial representation of the body (e.g. in parietal lobe – see next section) in CRPS patients is adaptive in that it re-directs attentional resources and slows decision time in order to gather more sensory evidence to make more informed decisions.

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

In sum, the patterns of altered late-latency SEP response in CRPS patients indicate that both endogenous and exogenous processes may interact to produce the observed performance decrements, namely longer response times.

Parietal lobe decrements in tactile processing in CRPS

Our analysis of SEPs and their sources at 124-132ms correspond to that commonly labelled as the N140 component of the SEP, which have been attributed to activity in SI and SII [39,40], as well as medial temporal (e.g. parahippocampal) regions, contralateral frontal cortex and insular cortex [39,40]. Our source results are in broad agreement with this previous literature, except for additional activation of superior parietal lobe (SPL) and precuneus in our study.

In CRPS patients compared to healthy controls, we found a similar augmentation (in terms of latency and scalp distribution) of the negative polarity potential at 132ms in Experiment 1 compared to that at 124ms in Experiment 2. On the other hand, in both experiments, CRPS patients (compared to healthy controls) displayed decrements in tactile processing in the precuneus and SPL, which are likely related to the smaller positivity in posterior midline electrodes observable at mid-latencies. Hence, a mid-latency shift was observed in patients away from parietal processing and towards frontal activity. The fact that parietal lobe decrements were observed in both experiments shows that it occurs independently of task demands.

Functional imaging findings suggest the SPL and precuneus have an important role in visuo-spatial representation [41]. Previously, research has found that precuneus is active during

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

tracking of spatial changes in visual stimuli [42] and processes visuo-tactile mismatch responses in concert with the medial temporal lobe [43]. Therefore, a plausible hypothesis is that reduced SPL and precuneus activity in tactile spatial tasks in patients with CRPS reflects deficits in visuo-spatial representations of the body. Behavioural characterisation of these cortical changes in future studies may be well served by measures of hand laterality recognition [44], on which performance is likely subserved by visuospatial functions.

Conclusion

There is an unmet need to better characterise CRPS patients in terms of underlying mechanisms to aid early detection and treatment. Our study confirms highly variable tactile discrimination performance across CRPS patients, and points to previously undiscovered cortical processes at mid-to-late latencies relating to some aspects of task performance. In particular, behavioural response times were linked to augmented late latency activity in SMA, and high between-subject variability in both measures indicate mechanistic heterogeneity in perceptual decision-making mechanisms. Further research is required to fully characterise the pathophysiology and compensatory mechanisms underlying tactile discrimination performance in CRPS. Future studies would benefit from larger sample sizes that can cluster patients into mechanistically homogeneous subgroups and test for differential prognosis and treatment responses in these subgroups.

References

1. Kuttikat, A. *et al.* Neurocognitive and Neuroplastic Mechanisms of Novel Clinical Signs

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

in CRPS. *Front. Hum. Neurosci.* **10,** 16 (2016).

2. Di Pietro, F. *et al.* Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *J. Pain* **14,** 1001–18 (2013).

3. Förderreuther, S., Sailer, U. & Straube, A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *Pain* **110,** 756–61 (2004).

4. Kuttikat, A., Shaikh, M., Oomatia, A., Parker, R. & Shenker, N. Novel Signs and their Clinical Utility in Diagnosing Complex Regional Pain Syndrome (CRPS) – A Prospective Observational Cohort Study. *Clin. J. Pain* 1 (2016). doi:10.1097/AJP.0000000000000434

5. Pleger, B. *et al.* Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. *Neuroimage* **32,** 503–10 (2006).

6. Maihöfner, C., Handwerker, H. O., Neundörfer, B. & Birklein, F. Cortical reorganization during recovery from complex regional pain syndrome. *Neurology* **63,** 693–701 (2004).

7. Maihöfner, C., Handwerker, H. O., Neundörfer, B. & Birklein, F. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology* **61,** 1707–15 (2003).

8. Pleger, B. *et al.* Mean sustained pain levels are linked to hemispherical side-to-side differences of primary somatosensory cortex in the complex regional pain syndrome I. *Exp. brain Res.* **155,** 115–9 (2004).

9. Juottonen, K. *et al.* Altered central sensorimotor processing in patients with complex regional pain syndrome. *Pain* **98,** 315–23 (2002).

10. Vartiainen, N. V, Kirveskari, E. & Forss, N. Central processing of tactile and nociceptive

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

stimuli in complex regional pain syndrome. *Clin. Neurophysiol.* **119,** 2380–8 (2008).

11. DeMirci, S. & Savas, S. The auditory event related potentials in episodic and chronic pain sufferers. *Eur. J. pain* **6,** 239–244 (2002).

12. Tandon, O. P., Kumar, A., Dhar, D. & Battacharya, A. Event-related evoked potential responses (P 300) following epidural methylprednisolone therapy in chronic low back pain patients. *Anaesthesia* **52,** 1173–6 (1997).

13. Karl, A., Diers, M. & Flor, H. P300-amplitudes in upper limb amputees with and without phantom limb pain in a visual oddball paradigm. *Pain* **110,** 40–8 (2004).

14. Turetsky, B. I. *et al.* Neurophysiological Endophenotypes of Schizophrenia: The Viability of Selected Candidate Measures. *Schizophr. Bull.* **33,** 69–94 (2006).

15. Chennu, S. *et al.* Dissociable endogenous and exogenous attention in disorders of consciousness. *NeuroImage Clin.* **3,** 450–461 (2013).

16. Parra, M. a, Ascencio, L. L., Urquina, H. F., Manes, F. & Ibáñez, A. M. P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. *Front. Neurol.* **3,** 172 (2012).

17. Ramchurn, A., de Fockert, J. W., Mason, L., Darling, S. & Bunce, D. Intraindividual reaction time variability affects P300 amplitude rather than latency. *Front. Hum. Neurosci.* **8,** 557 (2014).

18. Polich, J. Updating P300: An Integrative Theory of P3a and P3b. *Clin. Neurophysiol.* **118,** 2128–2148 (2009).

19. Chennu, S. *et al.* Expectation and attention in hierarchical auditory prediction. *J. Neurosci.* **33,** 11194–205 (2013).

20. Carbine, K. A. Sample size calculations in human electrophysiology (EEG and ERP)

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

studies: A systematic review and recommendations for increased rigor. *Int. J. Psychophysiol.* **111,** 33–41 (2017).

21. Harden, R. N., Bruehl, S., Stanton-Hicks, M. & Wilson, P. R. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med.* **8,** 326–31 (2007).

22. Cleeland, C. S. & Ryan, K. M. Pain assessment: global use of the Brief Pain Inventory. *Ann. Acad. Med. Singapore* **23,** 129–138 (1994).

23. Stratford, P. W., Binkley, J. M. & Stratford, D. Development and initial validation of the upper extremity functional index. *Physiother. Canada* **53,** 259–267 (2001).

24. Binkley, J. M., Stratford, P. W., Lott, S. A. & Riddle, D. L. The Lower Extremity Functional Scale (LEFS): Scale Development , Measurement Properties , and Clinical Application. *Phys. Ther.* **79,** 371–383 (1999).

25. Galer, B. & Jensen, M. P. Neglect-like symptoms in CRPS.Results of a self-administered survey. *J. Pain Symptom Manage.* **18,** 213–217 (1999).

26. Snaith, R. P. Health and Quality of Life Outcomes. **4,** 6–9 (2003).

27. Duncan, C. C. *et al.* Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clin. Neurophysiol.* **120,** 1883–1908 (2009).

28. Delorme, A. & Makeig, S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* **134,** 9–21 (2004).

29. Bell, A. J. & Sejnowski, T. J. An information-maximization approach to blind separation and blind deconvolution. *Neural Comput.* **7,** 1129–59 (1995).

30. IBM. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. (2012).

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

31. Litvak, V. & Friston, K. Electromagnetic source reconstruction for group studies. *Neuroimage* **42,** 1490–1498 (2008).

32. Litvak, V. *et al.* EEG and MEG data analysis in SPM8. *Comput. Intell. Neurosci.* **2011,** 852961 (2011).

33. Comerchero, M. D. & Polich, J. P3a, perceptual distinctiveness, and stimulus modality. *Brain Res. Cogn. Brain Res.* **7,** 41–8 (1998).

34. Hinds, O. *et al.* Roles of default-mode network and supplementary motor area in human vigilance performance: evidence from real-time fMRI. *J. Neurophysiol.* **109,** (2013).

35. Romo, R. & Salinas, E. Flutter discrimination: neural codes, perception, memory and decision making. *Nat Rev Neurosci* **4,** 203–218 (2003).

36. Hernández, A., Zainos, A. & Romo, R. Temporal evolution of a decision-making process in medial premotor cortex. *Neuron* **33,** 959–972 (2002).

37. Preuschhof, C., Heekeren, H. R., Taskin, B., Schubert, T. & Villringer, A. Neural correlates of vibrotactile working memory in the human brain. *J. Neurosci.* **26,** 13231–13239 (2006).

38. Preuschhof, C., Heekeren, H. R., Taskin, B., Schubert, T. & Villringer, A. Neural correlates of vibrotactile working memory in the human brain. *J. Neurosci.* **26,** 13231–13239 (2006).

39. Valeriani, M., Fraioli, L., Ranghi, F. & Giaquinto, S. Dipolar source modeling of the P300 event-related potential after somatosensory stimulation. *Muscle and Nerve* **24,** 1677–1686 (2001).

40. Tarkka, I. M., Micheloyannis, S. & Stoki, D. S. Generators for human P300 elicited by

bioRxiv preprint doi: https://doi.org/10.1101/146613; this version posted June 7, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

somatosensory stimuli using multiple dipole source analysis. *Neuroscience* **75,** 275–287 (1996).

41. Cavanna, A. E. & Trimble, M. R. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* **129,** 564–583 (2006).

42. Meehan, S. K. & Staines, W. R. The effect of task-relevance on primary somatosensory cortex during continuous sensory-guided movement in the presence of bimodal competition. *Brain Res.* **1138,** 148–158 (2007).

43. Kitada, R., Sasaki, A. T., Okamoto, Y., Kochiyama, T. & Sadato, N. Role of the precuneus in the detection of incongruency between tactile and visual texture information: A functional MRI study. *Neuropsychologia* **64,** 252–262 (2014).

44. Moseley, G. L. Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology* **62,** 2182–6 (2004).