The "Gulf War syndrome". Is there evidence of dysfunction in the nervous system?

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Abstract
In a pilot study, 14 Gulf War veterans were randomly selected from a large list of those with unexplained illness, to compare the functional integrity of the peripheral and central nervous system with a group of 13 healthy civilian control subjects using predetermined outcome measures. The controls were matched closely for age, sex, handedness, and physical activity. Outcome measures included scoring of symptoms and clinical neurological signs, quantitative sensory testing of heat, cold and vibration sensibilities, motor and sensory nerve conduction studies on upper and lower limbs, needle EMG of distal and proximal muscles and multimodality evoked potential (visual, brainstem, and somatosensory) studies.

Three measurements, all related to peripheral nerve function (cold threshold ($P = 0.0002$), sural nerve latency ($P = 0.034$), and median nerve sensory action potential ($P = 0.030$)) were abnormal in the veterans compared with the controls. There may be a dysfunction in the veterans but more studies are required to investigate the findings further and to characterise the dysfunction if confirmed.

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There has been increasing public concern about the so-called Gulf War syndrome in veterans who participated in Operation Desert Storm in 1991. Many veterans were found to have diagnosable diseases but in many the symptoms were not readily explained and this bizarre collection of symptoms has been referred to as the Gulf War syndrome unexplained illness (GWSUI). The symptoms include excessive fatigue, sensory symptoms such as paraesthesiae and numbness, headaches, skin rashes, myalgia, arthralgia, dyspnoea, chest pain, memory loss, sleep disturbances, and diarrhoea. Soldiers in the Gulf were given vaccines against polio, hepatitis B, anthrax, yellow fever, and cholera. They were also prescribed tablets known as NAPTS and BATS with the aim of protecting them against the potential use of chemical and biological weapons during the war. These tablets contain pyridostigmine bromide and pentavalent botulinum toxoid respectively. A recent study showed that giving pyridostigmine at the equivalent prescribed dose to the soldiers caused a breakdown of skeletal muscles after physical exercise in rats. There is also evidence that troops were exposed to pesticides during the war which have potential neurotoxic effects. Furthermore, although the toxic and biological effects of each substance are well identified, their combined effects are not.

It is desirable to establish whether or not there is any scientific evidence of organic neurological dysfunction underlying this syndrome given the nature of the symptoms reported. This pilot study was designed to look for any evidence of peripheral and central nervous system dysfunction in veterans with GWSUI. The neurological symptoms and clinical signs were scored by standard methods and a battery of neurophysiological techniques was used to assess the function of both the peripheral and the central nervous system in a group of 14 soldiers, randomly selected, and in a group of age and sex matched control subjects. These neurophysiological techniques are sufficiently sensitive to detect early or subclinical signs of neurotoxicity in humans. 

Subjects and methods
Fourteen veterans were investigated, 12 men and two women, all of whom had taken part in the Gulf War and who complained of unexplained illness afterwards. These soldiers were randomly selected by a standard computer program (Lotus 1–2–3 using a congruential multiplicative generator) from a list of 40 veterans from all over the United Kingdom with GWSUI, made available to us by a voluntary organisation. All the subjects selected by computer were studied and none were rejected for other reasons. The mean age was 34.2 (SD 8.0); range 24–50 years. They had no known causes of peripheral nerve dysfunction, no family history of neuromuscular illnesses, and none were on any neurotoxic medication or excessive alcohol intake. Thirteen healthy
civilian control subjects (mean age 35.1 (SD 7.8); range 23–49 years) matched for age, sex, handedness, and as closely as possible for physical activity (similar quality and average hours of daily physical exercise) were also studied. The controls were not matched for height or weight. The study had been approved by the local hospital ethics committees and all those participating gave their informed consent.

The symptoms and signs were scored according to international standard techniques. Clinical symptoms were scored as: 0: absent; 1: present without further quantification. Symptoms included fatigability, weakness, paraesthesiae, numbness, spontaneous sensation of heat and cold, and pain with an overall symptom score ranging from 0 to 6. Five reflexes (biceps, triceps, supinator, knee, and ankle) were scored on the right side. Each reflex was graded 0: normal, 1: present only on reinforcement and 2: absent, thereby providing an overall reflex score ranging from 0 to 10. Power in the distal, intermediate, and proximal group of muscles in the right upper and lower limbs was assessed and scored ranging from 0: normal to 4: complete paralysis using the same criteria as the MRC scale and was combined into an overall score ranging from 0 to 24. Sensations of pin prick, vibration, fine touch, and position on the right side were scored separately as follows: 0: normal, 1: reduced below ankle, 2: reduced below knee, 3: reduced in hand and below knee and 4: reduced below elbow and below knee. These were combined into a single score ranging from 0 to 16 for each person.

Motor nerve conduction studies in the median and the common peroneal nerves and sensory conduction studies in the right median and sural nerves were carried out with standard techniques. The shortest distal motor latencies, fastest motor conduction velocities, compound muscle action potential amplitudes, shortest F wave latencies of 10 supramaximal stimulations, sensory latencies, and amplitudes were all measured. Needle EMG was performed in the right tibialis anterior and extensor digitorum brevis muscles.

Quantitative sensory testing was undertaken by measuring thermal thresholds (heat and cold) on the dorsum of the right foot and vibration threshold over the middle of the right first metatarsal bone. The first two assess the small fibre afferent pathways and the last tests the large fibre afferent pathways. Pattern reversal visual, brainstem auditory, and somatosensory evoked potentials (to stimulation of the right median nerve at the wrist) were recorded with standard techniques.

The clinical assessments and the battery of neurophysiological investigations were performed by three independent teams with no prior knowledge of each others’ outcome for both the patients and the control subjects.

The median and the 25 and 75 percentiles are given for the quantitative sensory testing data which were not normally distributed and the statistical significance was evaluated by the Mann–Whitney U test. The remitting neurophysiological variables, which were normally distributed, are described in terms of their mean values, SE, and 95% confidence interval of the control mean. The statistical significance of the difference in mean values between the control and veteran groups were calculated by two tailed Student’s t test.

### Results

The table shows a summary of the results. In the patient group, the symptom score was increased (P = 0.00002) as was the mean score for clinical signs although at a lower level of significance (P = 0.0198). The cold sensation threshold was raised (P = 0.00018). The mean sural sensory potential latency was increased in the patient population (P = 0.034) whereas the mean amplitude of the sensory potential recorded from the median nerve was reduced (P = 0.030). Neither the needle EMG investigation nor any of the evoked potential variables showed convincing evidence of abnormality.

### Discussion

The difference between the two populations in terms of symptom scoring, although large (P = 0.00002), is non-specific and can only be relevant if accompanied by abnormalities in the objective variables. It is interesting to note that the mean scores of clinical neurological signs showed a significant difference with a P value of 0.0198. In addition, two variables...
from sensory nerve conduction studies, both testing large fibre peripheral nerve function, were significantly different (P = 0.030 and 0.034). One of the quantitative sensory testing variables (cold threshold, testing thinly myelinated small fibre function) was abnormal (P = 0.00018).

In performing multiple statistical tests on a set of variables, there is a risk that some of the comparisons will be statistically significant purely by chance. After applying the Bonferroni correction factor,2 two of the tests remained significantly different at the 95% confidence level. It is therefore unlikely that the differences found between the two study populations occurred at random, and raises the question of possible organic elements underlying some of the complaints in the patient group. The exact clinical relevance of these findings is unknown and further studies of larger groups are required for verification and to characterise the nature and cause of any dysfunction found.

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