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The impact of the 1991 Gulf War on the mind and brain: findings from neuropsychological and neuroimaging research

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Many veterans of the 1991 Gulf War (GW) have complained of somatic and cognitive symptoms that may be neurological in nature. However, whether or not changes in brain function are associated with GW service continues to be debated. Studies of GW veterans using objective, performance-based neuropsychological measures have yielded inconsistent findings, with those indicating deficits among GW veterans typically revealing only relatively mild levels of neuropsychological impairment. Further, performances on objective neuropsychological tasks show little correspondence to subjective perceptions of cognitive functioning. Although preliminary magnetic resonance spectroscopy (MRS) studies demonstrate reduced *N*-acetylaspartate-to-creatine (NAA/Cr) ratio in select brain regions among GW veterans who report health concerns, this work requires further replication with larger, more representative samples. There is no evidence from neuroimaging studies of a non-specific effect of GW service or of changes in brain structure or function related to health status when conventional radiological methods are used. Owing to the paucity of objective exposure, baseline health data, and the now significant time elapsed since the GW, aetiological issues may never be fully resolved. Therefore, research addressing clinical management of GW veterans with neuropsychological dysfunction and neuroimaging abnormalities may prove more fruitful than exclusive focus on aetiology.

Keywords: Gulf War; neuropsychological functioning; neuroimaging; cognition; brain

The potential impact of 1991 Gulf War (GW) participation on the mind and brain has received considerable attention, but remains controversial (Iowa Persian Gulf Study Group 1997; Unwin *et al.* 1999; Kang *et al.* 2000; Cherry *et al.* 2001; Unwin *et al.* 2002). GW veterans have complained of a number of symptoms that could be directly or indirectly related to changes in brain function, including memory loss, slurred speech, dizziness, tremor, rigidity, headache, concentration problems, fatigue and lack of energy (Iowa Persian Gulf Study Group 1997; Unwin *et al.* 1999; Kang *et al.* 2000; Cherry *et al.* 2001; Unwin *et al.* 2002). Neuropsychological symptoms such as memory and concentration problems have been among the most commonly reported health complaints of GW veterans. For example, 24.1% of individuals in the US Veterans Affairs (VA) Registry Health Examination Program (Murphy *et al.* 1999) and 36.2% of individuals in the US Department of Defense (DoD) Comprehensive Clinical Evaluation Program (Joseph & Team 1997) reported memory problems, making memory impairment the fourth most common complaint across the two programs (DVA & DOD 2002). Similarly, both the North American and European GW veteran cohorts have consistently reported cognitive dysfunction at greater frequencies than non-deployed comparison samples (Iowa Persian Gulf Study Group 1997; Unwin *et al.* 1999), with neuropsychological symptoms ranking among the top five health complaints of GW veterans in several of these large-scale epidemiological surveys (Fukuda *et al.* 1998; Goss Gilroy 1998; Proctor *et al.* 1998; Gray *et al.* 1999; Ishoy *et al.* 1999; Gray *et al.* 2002; Simmons *et al.* 2004).

Often taken as an index of brain integrity, the frequency of cognitive complaints among GW veterans has raised alarms in relation to GW illnesses because of the potential links between neuropsychological functioning and suspected neurotoxicant exposures. Among the environmental hazards postulated as aetiologic factors for GW-related illnesses, several have known or strongly suspected neurotoxic properties. These include organophosphate pesticides, chemical warfare agents, solvents and pyridostigmine bromide (PB; Joseph *et al.* 1998), as well as depleted uranium (McDiarmid *et al.* 2000). As an index event, the bombing of the chemical warfare facility at Khamisiyah is estimated to have potentially led to low-concentration exposures of sarin/cyclosarin in over 100 000 troops and has recently been linked to increased risk of brain cancer (Bullman *et al.* 2005). However, memory and concentration complaints tend to be non-specific and may be associated with a range of clinical presentations other than traditional neurological disorders and neurotoxic syndromes, including

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natural intra- and inter-individual variation, neurodevelopmental disorders and psychiatric disorders (Binder & Campbell 2004). Further, cognitive complaints may be subjected to reporting biases and do not necessarily correspond to objective, cognitive performances (e.g. Binder *et al.* 1999). Thus, much of the controversy surrounding these symptoms centres on aetiological mechanisms and whether neuropsychological complaints correspond to the underlying brain dysfunction.

Traditional neurotoxicology research emphasizes dose–response relationships in which higher levels of toxicant exposure are associated with more severe and more persistent central nervous system (CNS) compromise. However, with rare exception, exposure levels for known GW toxicants have been difficult to document retrospectively, and some war-zone toxic exposures possibly remain unknown. Compounding the difficulty of assessing causal relationships, baseline (pre-deployment) measurements of brain integrity are absent, making it difficult to exclude the possibility of pre-existing symptoms or vulnerabilities. As with other aspects of unexplained GW illnesses, the lack of objectively measured exposures combined with the absence of objective, prospective measures of baseline functioning has led to a variety of sampling and methodological approaches, each with strengths and weaknesses. Nonetheless, sophisticated neuropsychological and neuroimaging methods have been applied to assessment of CNS outcomes in GW veterans. Below, we review the findings of these studies, integrating discussion of potential mechanisms for brain and neuropsychological dysfunction in GW veterans and interpretive limitations inherent to the methodologies.

1. PERFORMANCE-BASED NEUROPSYCHOLOGICAL OUTCOMES OF GW DEPLOYMENT

Studies using performance-based measures to examine neuropsychological outcomes of GW participation have adopted two primary design strategies: (i) comparison of deployed GW veterans to non-GW deployed samples or normative data and (ii) comparison of high-risk to low-risk subgroups of deployed GW veterans. Whereas performance-based measures of neuropsychological functioning hold the advantage of increased objectivity as compared to self-report data, performance-based measures present additional challenges to research feasibility due to greater time demands per participant and the typical standard of individual, in-person administration in controlled environments. Thus, as compared to studies focusing on self-reported outcome data derived from surveys, studies incorporating performance-based measures of neuropsychological outcomes are more likely to have used smaller, regionally recruited or convenience samples, with the exception of a few studies (David *et al.* 2002; Proctor *et al.* 2003).

We have organized our review of the neuropsychological literature according to the key questions relevant to understand the nature and origin of neuropsychological deficits in GW veterans. We begin with the most basic question. Does simply having been deployed to the GW lead to neuropsychological compromise? We then turn to the examination of potential risk factors within the deployment environment or within the individual, including examination of subgroups of deployed veterans at potentially elevated risk for neuropsychological impairment. Finally, we examine the relationship between self-reported neuropsychological symptoms and objective performances.

(a) *Does GW deployment in and of itself lead to neuropsychological impairment?*

Early studies of GW neuropsychological outcomes relied on demographically equivalent civilian samples (Goldstein *et al.* 1996) or normative data (Axelrod & Milner 1997) as comparators to GW veterans. These studies, using relatively small sample sizes, revealed only weak associations between deployment and neuropsychological performance. Comparing 21 US Gulf-deployed veterans recruited from a local GW registry to 38 non-veterans on an abbreviated neuropsychological battery developed for neurotoxicology research, Goldstein *et al.* (1996) found that Gulf-deployed veterans showed more impairment on an index score, but group differences were not maintained when the analysis was adjusted for emotional functioning. Although unadjusted, univariate comparisons of specific neuropsychological measures revealed minimal group differences, when chance was controlled via multivariate comparison of the 14 individual measures, the comparison failed to reveal group differences. Axelrod & Milner (1997) also found weak association between GW deployment and neuropsychological impairment among 44 GW veterans recruited from a US Army National Guard (ARNG) unit 2 years following their return from the Gulf. As compared to normative data, performance was impaired only on fine motor tasks and the Stroop (an attentional task requiring selective focus on the perceptual aspects of stimuli in the face of competing semantic information). In contrast, performances were within normal limits on intellectual, memory, verbal, executive, grip strength and other attentional tasks.

Later studies employing somewhat larger samples, including veteran comparison groups, likewise revealed only minimal cognitive compromise attributable to GW deployment. For example, using a stratified sampling procedure in which deployed participants were selected from larger cohorts to assure equal numbers of high and low-symptom reporters and oversampling of women, White *et al.* (2001) compared the neuropsychological performances of regionally recruited GW-deployed US ARNG and Reservist veterans ($n=193$) drawn from the Fort Devens (north-eastern US) and South Louisiana cohorts to the performances of regionally recruited (Maine ARNG) veterans deployed contemporaneously to Germany ($n=47$). Examining over 40 variables derived from neuropsychological tasks selected on the basis of sensitivity to neurotoxicant exposure, group differences (adjusted for age, education, gender and sampling design) emerged on a few selected measures of memory recall and mental tracking, and there was a general trend for the performances of Germany-deployed veterans to be more proficient than

Gulf-deployed veterans. However, the direction of these non-significant group differences was not uniform and, once the significance levels were adjusted for multiple comparisons, no group differences emerged except those indicating greater disturbances of state affect among Gulf-deployed veterans.

Vasterling *et al.* (2003) examined a sensory measure (i.e. olfactory identification) and other indices of neuropsychological functioning thought to be sensitive to neurotoxicant exposure in 72 Gulf-deployed and 33 non-deployed GW-era veterans community-recruited from the South Louisiana cohort an average of 9 years following their return from the Gulf. Group comparisons covarying for age and rank failed to reveal performance differences as a function of deployment status on either the olfactory task or any other neuropsychological measure (regardless of adjustment for multiple comparisons). Moreover, it was difficult to attribute the failure to detect group differences in this study to insufficient sample size, as demonstrated by extremely small standard units of difference generated by a power analysis.

In the only study targeting a pure treatment-seeking sample, Sullivan *et al.* (2003) compared 207 US GW veterans to 57 non-deployed GW-era veterans on their performances on a large battery of neuropsychological tests. Following methodological adjustments for chance findings, age and gender, results revealed that GW veterans performed less proficiently than their non-deployed counterparts on an attentional task (digit span), a visuospatial construction task (block construction) and a visual memory task, in addition to reporting greater mood disturbance. However, because over half of the GW-deployed veterans were recruited from lists of patients referred specifically for neuropsychological evaluation, as opposed to the non-deployed veterans who were recruited from other contexts, the GW-deployed group may have been somewhat biased in favour of neuropsychological compromise strictly as a function of differential recruiting procedures.

Two studies examining European Gulf-deployed cohorts produced findings generally consistent with those of US studies, indicating minimal association between deployment to the Gulf and neuropsychological impairment. Sampling from a large population-based UK cohort, David *et al.* (2002) created six groups of veterans on the basis of deployment location (Gulf, Bosnia, non-deployed Gulf-era) and symptom reporting (ill, healthy) and administered a comprehensive battery of performance-based neuropsychological tasks. Factorial analyses crossing deployment location with symptom reporting and adjusted for age, education and estimated native cognitive potential revealed in regard to deployment status that (i) Gulf-deployed veterans performed more poorly than non-deployed Gulf-era veterans on verbal and performance intellectual index scores and (ii) Gulf-deployed veterans performed less proficiently than all other deployment groups on a task of fine motor speed and dexterity (Purdue pegboard). After covarying for depression, group differences remained in verbal IQ and pegboard performances. However, once analyses were adjusted for multiple comparisons, no deployment-related differences remained. Further, analyses failed to produce an interaction between deployment and health symptom reporting.

Finally, Proctor *et al.* (2003) studied Danish troops deployed to the Gulf region. As an interesting extension of studies of American and British troops, Danish troops had been deployed as peacekeepers following cessation of the major military offensive and, therefore, unlike the American and the British troops, were not subject to combat, SCUD missiles, or ingestion of anti-nerve gas pills. Like the studies of the American and the British troops, multivariate analysis adjusted for age did not reveal differences between deployed and non-deployed troops on neuropsychological tasks selected for their sensitivity to neurotoxicant exposures, although univariate analyses unadjusted for multiple comparisons revealed very small differences on selected measures of executive functioning and verbal memory.

In summary, comparisons of deployed to non-deployed GW veterans without any further differentiation beyond deployment status have revealed only minimal group differences. Those studies indicating Gulf-related performance decrements suggested slightly poorer performance on select neuropsychological tasks by Gulf-deployed troops as compared to non-deployed and other location-deployed troops, as compared to normative data. However, the neuropsychological deficits associated with GW deployment varied across studies, and such findings only rarely withstood the rigour of adjustment for multiple comparisons or other factors (e.g. emotional functioning) potentially contributing to neuropsychological performance deficits. Nonetheless, the minimal differences that did emerge when deployment was examined as a predictive factor raise the question of whether more pronounced deficits would emerge if specific subgroups at elevated risk for neuropsychological compromise were identified. In other words, it may be that if not all deployed personnel underwent the same GW experiences or were not otherwise at equal risk for neuropsychological impairment, examining the broader population of deployed veterans without subgrouping these veterans in a meaningful way could potentially mask relationships between critical GW-related factors and neuropsychological impairment.

(b) *Are specific subgroups of GW veterans at elevated risk for neuropsychological impairment?*

To address possible differential performance among GW subsets, investigators have attempted to examine several factors that may have placed GW veterans at elevated risk for neuropsychological impairment, including environmental exposures, unexplained illnesses, stress-related psychopathology and motivational factors.

(i) *Impact of environmental exposures*

As summarized above, although a number of neurotoxicants have been implicated as aetiologic factors for GW-related cognitive complaints, minimal objective exposure data exist, making it difficult to assess dose–response relationships. Therefore, a handful of GW studies have relied on self-reported exposures as proxies for actual exposure data to examine

exposure–symptom relationships, with only one published study to date examining the association of an objective exposure (depleted uranium) to neuropsychological dysfunction.

Perhaps providing the strongest evidence of links between self-reported exposure and neuropsychological impairment, White *et al.* (2001) demonstrated that self-reported pesticide exposure among 153 GW veterans was associated with select neuropsychological variables. These variables, derived from a much larger variable set, included the delayed recall condition of a visual reproduction test, the second of five learning trials and the short-delayed recall condition of a verbal list learning task, a working memory task requiring recitation of digits in reverse order (digit span backward), and measures of state affect. Drawing from the same sample, Lindem *et al.* (2003*a*) reanalysed the data, creating a binary (yes/no) exposure variable that reflected self-reported exposure to any of eight potential GW hazards. To examine the relative contributions of post-traumatic stress disorder (PTSD) symptom severity and self-reported exposure to neuropsychological outcomes, the data were subjected to a regression analysis, adjusted for age, education and estimated native intellectual potential. Findings indicated that whereas PTSD symptom severity was associated with neuropsychological performances on a wide range of neuropsychological tasks, self-reported hazards exposures were associated only with select neuropsychological variables (i.e. sustained attention, finger tapping speed, verbal learning and the multiple choice condition of a visual memory task) in addition to measures of state affect.

Sullivan *et al.* (2003) found that among the 139 treatment-seeking GW veterans, those reporting exposure to PB, an anti-nerve gas agent, performed more poorly on a single measure derived from a card-sorting task than did veterans not reporting PB exposure. Using a factorial design in which self-reported PB exposure status was crossed with PTSD diagnostic status, results did not reveal main effects for PB exposure on other measures of neuropsychological functioning (including those assessing state affect) or interactions between PTSD and PB status. The emergence of a main effect for exposure on only a single measure (card sorting) in the context of multiple outcome variables raises the question that this finding could be attributable to chance.

The results of two other studies provided even less-compelling evidence in favour of exposure-related neuropsychological deficits. Vasterling *et al.* (2003) compared 26 veterans reporting high levels of exposure to GW environmental hazards to 46 veterans reporting low or no exposure to GW environmental hazards. Findings revealed that although veterans in the high-exposure group reported significantly greater trouble with new learning, blank spots in memory, forgetfulness and difficulty concentrating than the low-exposure group, the two exposure groups failed to differ on an olfactory identification task, several card sorting and working memory measures, measures of verbal and visual learning and memory and fine motor measures (pegboard performance). A power analysis indicated that insufficient sample size was unlikely to explain the pattern of results. Sillanpaa *et al.* (1997) similarly examined neuropsychological performance in relation to several deployment-related experiences in 82 GW veterans referred for clinical neuropsychological evaluation. Findings failed to reveal associations between a cumulative index of self-reported GW hazard exposures and performances on a comprehensive battery of neuropsychological tasks. However, for both of Vasterling *et al.* and Sillanpaa *et al.* studies, it could be argued that trends associated with specific neurotoxicant exposures were diluted by creating cumulative exposure indexes reflecting a mix of exposures, some of which may have had minimal impact on neuropsychological functioning.

In the only published study of neuropsychological functioning to examine objective GW exposure data, McDiarmid *et al.* (2000) compared the neuropsychological performances of 29 US depleted uranium (DU)-exposed to 38 non-DU-exposed GW veterans equated for age and military rank. Regression analyses indicated that 7 years after DU exposure, urine uranium levels were associated with scores on an impairment index derived from an automated neuropsychological battery measuring processing efficiency, but were not associated with scores on an impairment index derived from a more traditional neuropsychological battery. The findings are provocative, suggesting links between a specific exposure (DU) and neuropsychological performance. However, conclusions are tempered due to the conflicting results derived from the two individual impairment indexes, the inherent limitations associated with the use of single variable impairment index scores in some contexts, and the use of unspecified decision rules for determining impairment on tasks without normative data. Nonetheless, the study provides an important model of using objective exposure data to examine neuropsychological functioning in GW veterans and highlights the need for such an approach when objective exposure data are available.

In summary, there is mixed evidence regarding the relationship between self-reported exposures to GW environmental hazards and neuropsychological performances. Those studies documenting an association between self-reported exposure and neuropsychological performance have only done so on select variables drawn from much larger variable sets and have not shown a consistent pattern across reports of the specific neuropsychological measures associated with exposures, thus raising the question of spurious findings. On the other hand, the two studies failing to reveal such relationships used cumulative exposure indices, possibly inadvertently missing links between specific types of self-reported exposures and neuropsychological performances.

Perhaps more germane to the question is the degree to which self-report is a valid index of GW neurotoxicant exposure. Given that, even at the time of possible exposure, military personnel had little way of knowing whether they were exposed to several of the suspected GW neurotoxicants, self-reported exposures may be particularly unreliable in some cases. Consistent with this hypothesis, studies examining exposure reporting patterns have revealed poor longitudinal reliability of

self-reported GW hazard exposures and lack of validation using clinical examination of self-reported health symptoms among GW veterans (McCauley *et al.* 1999; Wessely *et al.* 2003). Only one study incorporated objective exposure among a small group of DU-exposed veterans, providing inconclusive evidence of links between DU and neuropsychological performance. However, this study serves as a useful model for the rare cases in which GW exposure data do exist. Given the recent links between proximity to the Khamisiyah munitions explosion and prevalence of brain cancer (Bullman *et al.* 2005), comparison of neuropsychological functioning in veterans proximal to the explosion to appropriately selected non-exposed GW veterans might prove informative.

(ii) *Relationship to unexplained illnesses*

Recognizing the lack of adequate exposure data and that health risks may not have been uniform across the entire population of GW-deployed military personnel, investigators focused their attention on sub-grouping GW veterans according to health symptom complaints. This group of studies has perhaps yielded the most consistent evidence that subgroups of GW veterans may be at elevated risk of neuropsychological impairment.

Haley *et al.* (1997*a*) and Hom *et al.* (1997) studied military personnel from the 24th Reserve Naval Mobile Construction Battalion who had participated in a larger epidemiologic survey (Haley *et al.* 1997*b*) of health symptoms. Based on the survey results, the investigators identified three primary (Syndrome 1—'Impaired Cognition'; Syndrome 2—'Confusion–ataxia'; and Syndrome 3—'Arthro-myo-neuropathy') and three overlapping (Syndrome 4—'Phobia–apraxia'; Syndrome 5—'Fever–adenopathy', and Syndrome 6—'Weakness–incontinence') factor-derived syndromes interpreted as relevant to neurological injury. For the neuropsychological study, the investigators selected the 26 GW veterans with the highest factor scores to comprise a 'Gulf War Syndrome' (GWS) group. The control group was comprised of 20 members of the same military unit, 10 who were deployed and reported no serious health problems and 10 who did not deploy to the Gulf during the war. Administering perhaps the most extensive neuropsychological battery of any study examining neuropsychological functioning in GW veterans, the investigators found that the GW Syndrome group performed more poorly than the control group on several index measures of generalized brain functioning (e.g. Halstead impairment index, intellectual test index scores) and several specific neuropsychological measures, including an executive category task, a visuomotor tracking task (trails B), grip strength (bilaterally), common sense verbal reasoning and vocabulary intellectual tasks, two sensory-perceptual tasks and a left–right orientation task. As the authors point out, taking into account both statistically significant and non-significant group comparisons, the mean performance of the ill group was less proficient than that of the non-ill group on 59 of 71 measures. However, using one-tailed tests of significance, 48 neuropsychological measures did not reach significance at the 0.05 level (including measures within the same domains as those found to be significant), and the authors did not adjust significance levels for multiple comparisons or include covariates. Thus, although the group comparisons revealed a general trend in the direction of impairment for the ill group, the actual performance differences between the two groups were relatively small.

The Portland Environmental Hazards Research Centre published a series of studies that built on each other as their cohort of GW veterans from the US Pacific Northwest grew (Anger *et al.* 1999; Storzbach *et al.* 2000; Binder *et al.* 2001; Storzbach *et al.* 2001). The neuropsychological studies sampled for symptomatic and asymptomatic subgroups, which were based on health survey responses combined with clinical examinations that permitted exclusion of medically explainable health symptoms. Sample sizes ranged from approximately 100 veterans divided into illness cases (those with unexplained health symptoms) and controls (those asymptomatic) in the earlier studies to over 350 veterans in the later studies. In sum, this series of studies revealed several findings relevant to symptomatic veterans: (i) following adjustment for military entrance examination scores, age, education and multiple comparisons, illness cases performed consistently less proficiently on a simple reaction time task and on an information processing task than healthy controls, but ill and healthy veterans did not differ on measures of attention or working memory, (ii) illness cases reported more emotional distress than controls and (iii) within the illness group, a subgroup with particularly slow times on the information processing task could be differentiated from non-slow cases and healthy controls on other neuropsychological tasks. The overall pattern of results suggested the existence of a specific subgroup of high health complaint veterans who were at particular risk for neuropsychological compromise, but that unexplained health complaints alone were not associated with more than minimal neuropsychological impairment.

Lange *et al.* (2001) examined neuropsychological performances in 48 American GW registry veterans with severe fatiguing illness and 39 healthy American GW registry veterans matched on IQ and equated for age, gender, race and alcohol use. After adjustment for multiple comparisons, findings indicated that ill veterans performed more poorly on attentional measures and an executive category abstraction task but did not differ from healthy veterans on measure of verbal or visual memory, fine motor dexterity or visual-perception. A regression analysis revealed that after accounting for the variance explained by mental disorders with post-war onset, both reaction time on the sustained attention task and performance on the executive category task remained associated with GW illness.

Finally, in the only nationally-sampled, population-based study examining ill and non-ill subsets, as described in the prior section, David *et al.* (2002) subdivided Gulf-deployed, Gulf-era-non-deployed and Bosnia-deployed British veterans into ill and healthy subsets based on their survey responses. Ill veterans scored lower on a performance IQ index and a digit-symbol coding task. However, after adjusting for

depression, the main effect for health status remained only for a single neuropsychological performance measure (i.e. digit-symbol coding), which was no longer significant when adjusted for multiple comparisons. Likewise, health status did not interact with deployment to produce neuropsychological performance deficits. When the Center for Disease Control definition of multi-symptom GW illness (Fukuda *et al.* 1998) was used to classify Gulf-deployed veterans into GW ill ($n=65$) and healthy ($n=33$) subsets, group comparisons adjusted for age, a pre-morbid estimate of intelligence and education revealed differences on several neuropsychological measures; but, after adjustment for depression, the two groups differed only on vocabulary and digit-symbol coding. After adjustment for multiple comparisons, no group differences remained on performance-based neuropsychological measures.

In summary, when Gulf-deployed veterans are grouped according to illness complaints, a weak but somewhat consistent pattern emerges in which veterans reporting health complaints perform more poorly on select neuropsychological tasks than healthy veterans. The work by the Portland group suggests that illness cases may be further divided into subgroups at relatively high or low risk for neuropsychological compromise based on slowing on a specific information processing task, but the mechanism accounting for elevated risk in this subgroup remains unknown. A question central to this group of cross-sectional studies is whether either the health symptoms reported by subgroups of these veterans or the associated neuropsychological deficits displayed by ill subgroups preceded GW deployment. A few studies tried to account for pre-GW functioning by using estimates of native cognitive potential as covariates. However, without baseline data, causal inferences are difficult to determine with any degree of certainty and point to the need for prospective work incorporating baseline assessment.

(iii) *Influence of stress-related psychopathology*

Psychological stress exposure and related emotional distress have been purported to elevate risk of neuropsychological compromise in GW veterans. This section focuses on the few neuropsychological studies that sampled specifically to over-represent subgroups of GW veterans with clinically significant mental disorder. The section briefly summarizes the results of studies from the preceding sections that examined the influence of psychiatric variables on the neuropsychological performances of GW veterans by accounting statistically for psychiatric and other emotional factors.

Each of the studies examining neuropsychological functioning among GW veterans with clinically significant mental disorders was characterized by convenience sampling, very small sample sizes and a focus on PTSD, and are therefore likely limited in their generalizability to the broader GW population. For example, Vasterling *et al.* (1997, 1998) found that physically healthy PTSD-diagnosed GW veterans performed more poorly on tasks of verbal intellectual functioning (including those thought to reflect premorbid functioning), sustained attention, mental manipulation and initial acquisition of new information than physically healthy GW veterans without mental disorders diagnoses. Sample sizes, however, were quite small, ranging from 18 to 19 PTSD-diagnosed veterans and 23 to 24 healthy controls. Nonetheless, findings were replicated using a Vietnam veteran sample (Vasterling *et al.* 2002), suggesting a consistent pattern of neuropsychological deficits associated with PTSD. Vythilingam *et al.* (2005) targeted memory functioning specifically and found that 14 physically healthy GW veterans with PTSD diagnoses performed less proficiently on both immediate and delayed retrieval conditions of visual and verbal anterograde memory tasks, and that these performances were correlated positively with hippocampal volume. However, no differences emerged between deployed and non-deployed veterans without PTSD diagnosis, arguing against an effect of GW service independent of mental health status. In contrast, when Sullivan *et al.* (2003) crossed PTSD diagnosis and self-reported PB exposure in a mixed group of somatically healthy and unhealthy treatment-seeking GW veterans, there were no main effects for PTSD among the 28 PTSD-diagnosed and 111 non-PTSD-diagnosed veterans. These results stand in contrast to other studies of PTSD, but may reflect sampling of treatment-seeking veterans and increased within-group variance due to the inclusion of both somatically healthy and unhealthy veterans.

The results of the Vasterling *et al.* and Vythilingham *et al.* studies are not very surprising, as they are consistent with a larger body of literature establishing links between PTSD diagnosis and neuropsychological performances across a number of military and civilian samples (see Bremner 2002; Vasterling & Brailey 2005, for reviews). However, they were not intended to, and do not fully, address links between GW participation and neuropsychological dysfunction for the following reasons. First, although war-zone deployment generally, and GW deployment specifically, is arguably stressful, *traumatic* exposure was not universal in the GW. Estimated PTSD prevalence rates rarely exceeding 16%, and not uncommonly failing to reach 10% (Stimpson *et al.* 2003), cannot fully account for the frequency of self-reported neuropsychological complaints among GW veterans. Conceptualizations of stress in the GW literature, sometimes failing to recognize the neurobiological implications of stress, have occasionally blurred the distinction between traumatic and non-traumatic stress. This has led to confusion, as traumatic and non-traumatic stress could each be hypothesized to affect CNS functioning differentially. Second, the studies reviewed above focused solely on PTSD and did not examine systematically the effects of other potentially stress-related mental disorders such as mood or non-PTSD anxiety disorders.

Studies that have accounted statistically for depression, PTSD symptoms and other non-PTSD stress symptoms (see previous sections) generally revealed that psychiatric and emotional factors overwhelmed health status in terms of utility in predicting neuropsychological compromise. Nonetheless, the results of Lange *et al.* (2001) and others (e.g. Sullivan

et al. 2003) suggest that psychiatric status cannot account entirely for neuropsychological compromise in GW veterans with health complaints. One of the major challenges in interpreting links between suspected neurotoxicant exposure, emotional distress and neuropsychological functioning is that, like severe stress exposures, some neurotoxicants are believed to affect subcortical limbic structures associated with emotion (Blokland 1996; White 2001). Therefore, in the absence of baseline data addressing emotional functioning, covariance of emotional distress may inadvertently parcel out an important exposure outcome (i.e. emotional dysfunction), as opposed to controlling for an aetiological mechanism of neuropsychological dysfunction (White 2003). In summary, it may be that stress-related and emotional factors account for neuropsychological dysfunction among some GW veterans, but there is not sufficient evidence to conclude that emotional disturbance is the sole explanatory factor for neuropsychological dysfunction among GW veterans.

(iv) *Can neuropsychological performance deficits in GW veterans be explained by motivational factors?*

Although performance-based neuropsychological tasks remove the subjective biases often associated with self-report surveys, performance on these tasks is partially dependent on adequate effort. However, GW studies have not uniformly taken effort into consideration. In the series of studies conducted by White and her colleagues, a screening version of a widely used neuropsychological measure of effort, the Test of Memory Motivation (TOMM; Tombaugh 1996), was administered to the majority of participants. Performance on TOMM, Trial 1 differed according to self-reported pesticide exposure in the Fort Devens/South Louisiana cohorts (White *et al.* 2001) and by deployment status in a sample of treatment-seeking veterans (Sullivan *et al.* 2003), but did not differ among deployed and non-deployed Danish veterans (Proctor *et al.* 2003) or between US GW-deployed and Germany-deployed veterans (White *et al.* 2001). Removal of participants scoring below a pre-determined cut-off on the TOMM (Sullivan *et al.* 2003) or entry of TOMM scores as covariates (White *et al.* 2001) did not alter the pattern of findings. Re-analysing data from the Fort Devens Gulf-deployed and Germany-deployed cohorts specifically to examine the influence of effort, Lindem *et al.* (2003*c*) found that GW-deployed participants scoring low on the TOMM performed less proficiently on three neuropsychological measures than GW-deployed participants who performed more proficiently on the TOMM. However, Gulf- and Germany-deployed participants did not differ on the TOMM, and rates of clinically significant sub-optimal performances were extremely low in both groups. Similarly, although the Portland group consistently found GW veterans with high-symptom complaints to perform more poorly than healthy controls on a forced-choice test of motivation, attention and memory (the Oregon Dual Task Procedure; Anger *et al.* 1999; Binder *et al.* 2001), performances fell within the range of adequate effort, and group differences were interpreted to reflect impairment of cognitive processes other than effort. Thus, when findings are taken together, insufficient effort does not appear to explain neuropsychological deficits in GW veterans.

(c) *How closely related are self-reported and performance-based indices of neuropsychological dysfunction?*

As described above, epidemiological survey and government registry data have consistently indicated that GW-deployed veterans report greater neuropsychological impairment than military veterans of the same era not deployed to the GW. However, performance-based neuropsychological deficits are much milder and less consistent across studies than would be predicted by the frequency and severity of subjective complaints of neuropsychological impairment among GW veterans. Because of this discrepancy, several studies specifically examined relationships between self-reported cognitive complaints and objective, performance-based measures among the same participants.

In general, studies directly examining correlations between subjective and objective neuropsychological measures have revealed little correspondence between the two. For example, Binder *et al.* (1999) found that subjective cognitive complaints were more closely related to psychological distress than to objective cognitive performances among 100 veterans with high health complaints who were recruited from the Portland Environmental Hazards Research Center cohort. Correlations between subjective cognitive complaints and specific objective performances on the Portland battery of attention, working memory, response time and information processing tasks were quite low, with correlation coefficients ranging from 0.03 to 0.28. Similarly, when 240 GW- and Germany-deployed troops were divided into high, moderate and low-symptom groups based on subjective neuropsychological complaints, the three groups did not differ on objective neurobehavioural tasks, although high symptom complaints were associated with greater affective disturbance (Lindem *et al.* 2003*b*). A similar pattern was revealed when the GW veterans were examined alone. Within specific samples, GW deployment, self-reported exposures and more general health complaints are associated with higher levels of subjective neuropsychological symptoms but correspond less closely to performance deficits on objective neuropsychological measures (Sillanpaa *et al.* 1997; David *et al.* 2002; Vasterling *et al.* 2003). This pattern mirrors a large epidemiological study of Australian GW veterans, who reported more neurological symptoms than a randomly sampled military comparison group but did not differ from the comparison group in neurological outcome based on objective physical signs (Kelsall *et al.* 2005). Chronic fatigue, also an as yet poorly understood syndrome, is similarly associated with divergence between subjective and objective indices of neuropsychological functioning (e.g. Grafman *et al.* 1993).

Does this mean that subjective complaints are invalid? The simple answer is 'not necessarily'. Such complaints indicate an identified functionally relevant problem area that may require clinical attention among

some veterans. In other words, if people report problems in their daily lives, there is a good chance that they experience those problems. However, the divergence of self-reported complaints with objective neuropsychological performances suggests that subjective complaints may have little correspondence to underlying brain dysfunction, assuming that the objective measures are adequately sensitive. In other words, it may be that subjective complaints and objective neuropsychological performance deficits reflect distinct underlying mechanisms. Thus, assessment of either subjective dysfunction or objective neuropsychological performance alone in GW veterans is probably insufficient, and each stands to provide a complementary perspective.

(v) *Neuroimaging research in GW veterans*

As summarized in an accompanying article (Rose & Brix 2006), several studies have addressed neurological functioning in GW veterans. Findings from these studies have provided some evidence of neurological dysfunction in GW veterans, including self-reported symptoms (e.g. Kang *et al.* 2002), findings from audiovestibular, neurophysiological and clinical examinations (e.g. Haley *et al.* 1997*a*), and elevated risk of amyotrophic lateral sclerosis (Horner *et al.* 2003; Coffman *et al.* 2005), although most objective studies of autonomic function, neurological examination, nerve conduction and neuromuscular functioning failed to reveal GW-related neurological dysfunction. Neuroimaging methodologies hold potential to complement neuropsychological methods and neurological examinations in investigating links between GW participation and brain functioning, serving as a source of converging data. However, relative to the neuropsychological GW literature, there has been only limited application of neuroimaging methods to the evaluation of neurological function in veterans with GW service.

In an early brain imaging study, Haley *et al.* (1997*a*) studied 23 veterans with GW syndromes (described above), 10 healthy deployed veterans and 10 healthy non-deployed veterans. Veterans underwent magnetic resonance imaging (MRI) T-1 and T-2 weighted structural imaging of the brain, and single photon emission computed tomography (SPECT) following injection of [Tc-99m] hexamethylpropyleneamine oxime (HMPAO) for measurement of at-rest brain blood flow with radiological interpretation of the scans. Although seven (30%) of GWS veterans and five (26%) of scanned non-GWS veterans had non-specific areas of increased T-2 signal intensity in subcortical white matter, the two groups did not differ significantly. Likewise, there were no group differences in abnormalities on SPECT scans of brain blood flow.

In a second study, Haley *et al.* (2000*b*) used magnetic resonance spectroscopy (MRS) to measure *N*-acetylaspartate-to-creatine (NAA/Cr) ratio, a measure of neuronal viability, in the basal ganglia. MRS was performed in 22 GW veterans who were recruited from the 24th Naval Reserve Mobile Construction Battalion and characterized by one of three factor analysis-derived syndromes: (i) impaired cognition; (ii) confusion–ataxia and (iii) central pain; 18 well veterans matched for age, sex and education level (control subjects); and 6 GW veterans with Syndrome 2 recruited from the local VA Medical Center. NAA/Cr was lower in the basal ganglia and brainstem of GW veterans with the three syndromes than in control subjects. Veterans with Syndrome 2 had decreased NAA/Cr in both the basal ganglia and the brainstem; those with Syndrome 1, in the basal ganglia only; and those with Syndrome 3, in the brainstem only (Haley *et al.* 2000*b*). A related MRS study (Haley *et al.* 2000*a*), examining neuronal mass via NAA/Cr ratios and dopamine production via the ratio of plasma homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) in 12 veterans with Syndrome 2 and 15 healthy veterans, indicated that neuronal mass in the left basal ganglia correlated negatively with central dopamine production across all participants.

Menon *et al.* (2004) studied 10 GW veterans with GWS, five GW veterans without physical complaints, and six healthy Vietnam veterans. The authors reported lower NAA/Cr ratio in the left and right hippocampus as measured with single voxel proton MRS in the GWS veterans compared to all non-GWS veterans, and compared to GW veterans without GWS. However, the method used to diagnose GWS was not described, and a subset of the GWS veterans had PTSD or depression. This is a limitation because PTSD and depression have been associated with smaller hippocampal volume (Kitayama *et al.* 2005). Also, the Vietnam veteran controls were at least 10 years older than the GWS veterans.

Vythilingam *et al.* (2005) examined hippocampal volume, hippocampal-mediated neuropsychological function, and cortisol response to a low-dose dexamethasone suppression test in deployed GW veterans with and without PTSD, non-deployed reservists, and healthy civilian subjects. Participants included 14 veterans (eight men, six women) with PTSD related to traumatic experiences during the GW, 23 (15 men, eight women) GW-deployed veterans without PTSD, 22 (nine men, 13 women) non-deployed GW-era veterans and 29 (nine men, 20 women) healthy civilians. The volume of the whole hippocampus, temporal lobe and whole brain was measured using coronal MRI images. Deployed veterans with PTSD, deployed veterans without PTSD, and non-deployed reservists had significantly smaller hippocampal volumes compared to healthy civilians. The head of the hippocampus was the only sub-region that differed significantly between veterans with PTSD and healthy civilians. Similar to the memory findings (described earlier), deployed and non-deployed GW-era veterans failed to differ in hippocampal volume, arguing against a non-specific effect of GW service on the brain. Moreover, civilians differed from non-deployed veterans, raising questions regarding the validity of the sole use of civilians as a comparison sample. Hippocampal volume correlated negatively with severity of childhood trauma but not with the severity of combat, suggesting that early trauma of chronic PTSD may be a more important determinant of smaller hippocampal volume than trauma related to GW service. Finally, salivary cortisol response to a low-dose dexamethasone suppression test did not differ significantly among the four groups. Consistent with this, Fujita *et al.* (2004) studied 19 GW veterans with

PTSD and compared them to 19 healthy age-matched non-deployed veterans. Benzodiazepine receptor binding was measured with SPECT and [I-123] Iomazenil imaging of the brain. Because benzodiazepine receptors are ubiquitous on neurons, their binding represents a good test of general neuronal viability. There were no group differences in benzodiazepine binding; however, among participants diagnosed with PTSD, childhood trauma correlated negatively with benzodiazepine receptor binding in the right superior temporal gyrus. This study did not report on GW-related somatic illness specifically; however, it argues against a non-specific effect of GW service on brain benzodiazepine binding.

2. SUMMARY AND CONCLUSIONS

Although neuropsychological and neurological symptoms are among the most common of GW health complaints, a specific neuropsychological or brain syndrome associated with GW service remains difficult to define. Neuropsychological studies have revealed an inconsistent pattern of results, with those studies suggestive of GW-related neuropsychological dysfunction indicating only mild levels of impairment that do not reliably converge with symptom reports. Mood disturbance is the most commonly affected domain in neuropsychological studies, but there is otherwise little consistency across neuropsychological studies regarding the domains or tasks most likely to be affected. Neuroimaging research using small, non-population-based samples has yielded preliminary evidence of reductions in neuronal viability in select brain regions among GW veterans with health complaints, but there is insufficient neuroimaging research to draw conclusions at this point. Of the few neuroimaging studies conducted, none revealed evidence of a non-specific effect of GW service on brain function or structure. Furthermore, in veterans with GW-related health complaints, there are no changes in brain structure or function that are visible with conventional radiology examinations. Single studies with MRS have shown findings that are interpretable as indicating reductions in neuronal viability (NAA/Cr ratio) in the hippocampus and basal ganglia in veterans with GW service and health complaints. However, studies using larger, more representative samples are needed to replicate these initial reports. In addition, neuroimaging studies controlling for stress-related psychiatric disorders or symptoms would be a critical methodological advancement.

Within the GW literature addressing objective neuropsychological impairment, researchers have examined various facets of GW participation as potential contributing factors. These include GW deployment as a non-specific factor, neurotoxicant exposures, unexplained illnesses, stress-related psychopathology and motivational factors. Although findings are not fully uniform, several conclusions from this literature can be derived.

First, there is little evidence that GW deployment alone poses significant risk of objective neuropsychological compromise. That is, studies comparing GW-deployed veterans to appropriate non-deployed comparison samples have not provided compelling evidence of deployment-related neuropsychological abnormalities. As summarized above, this finding is consistent with the few neuroimaging studies that have examined the non-specific effects of GW deployment. The lack of a non-specific GW deployment effect is not surprising, however, given the potential diversity of exposures, experiences and individual characteristics that comprise the deployed GW population.

Second, although self-reported exposures to GW environmental hazards have been associated with neuropsychological performance deficits, findings vary considerably across studies, and the validity of self-reported exposures has been questioned. There is only one published GW neuropsychological outcome study (McDiarmid *et al.* 2000) that documented exposure (to depleted uranium) objectively. This study serves as a useful model and provides evidence of neuropsychological dysfunction on a single index score. However, results should be considered preliminary and warrant further replication.

Third, self-reported illness appears in some cases to be associated with neuropsychological compromise. Correspondingly, the few neuroimaging studies suggestive of GW-related neural dysfunction grouped participants according to health complaints. However, without baseline information, the possibility that health symptoms and associated neural dysfunction predated the GW cannot be excluded. Nonetheless, such studies are useful in identifying subsets of GW veterans that are at heightened risk for neuropsychological compromise and require enhanced clinical care.

Finally, regarding emotional functioning and motivational factors, a handful of studies have documented links between PTSD neuropsychological deficits (and early childhood trauma and neuroimaging deficits) in GW veterans. However, the prevalence rates of PTSD in the GW population are sufficiently low that PTSD alone cannot explain the neuropsychological symptoms reported by GW veterans (Wolfe *et al.* 1999). In contrast, more generalized emotional distress not necessarily meeting criteria for a mental disorder may be more common among GW veterans (e.g. Perconte *et al.* 1993; Sutker *et al.* 1993; Holmes *et al.* 1998; Unwin *et al.* 1999), and studies examining associations between continuous measures of emotional distress, in particular depression, have revealed associations between distress and objective neuropsychological performances. Such associations in the context of potential neurotoxicant exposure pose interpretive challenges, as some neurotoxicants affect the limbic system, resulting in emotional dysfunction, whereas emotional disturbances in the absence of neurotoxicant exposures can be associated with both neural compromise and health problems more generally (Wolfe *et al.* 2002; Boscarino 2004; Schnurr & Green 2004). In contrast to emotional factors, which have shown some association with neuropsychological compromise, there is no evidence that insufficient motivation contributes to neuropsychological performance deficits in GW veterans.

Conclusions regarding etiological factors for brain dysfunction in GW veterans will continue to be hampered by almost entirely unavoidable methodological factors inherent to this research area, including

the paucity of objective exposure data, the absence of baseline data, and, in many cases, the significant time that has now elapsed between GW participation and assessment of neural functioning using objective neuropsychological and brain imaging techniques. The divergence between subjective and objective indices of neuropsychological functioning highlights the necessity of using performance-based measures of neuropsychological integrity, as well as self-reported symptoms. To the extent that exposure data become available, the field would benefit from viewing neuropsychological and brain imaging data in the context of specific known, objectively verified exposures. Similarly, if archival records addressing baseline functioning were available, such information would be useful in evaluating the possibility that pre-existing vulnerability factors contributed to health dysfunction following GW participation. Finally, genetic vulnerabilities and their interaction with environmental and stress exposures can be examined in the absence of baseline data through retrospectively collected genotypic data.

Thus, the current methodological challenges do not necessarily imply that research efforts addressing neural functioning in GW veterans should be abandoned, but rather that new approaches should be considered. Specifically, exclusive focus on single aetiologies has led to 'straw man' arguments that are divisive and in many cases counterproductive. More fruitful endeavours will likely include research questions that build on more complex models incorporating individual vulnerabilities, environmental factors and their physiological and emotional consequences and immunologic functioning. Such models have been applied to other 'medically unexplained' syndromes such as chronic fatigue and multiple chemical sensitivities (Binder & Campbell 2004). Ultimately, however, the goal must be to address identification and clinical management of those subsets of GW veterans at greatest risk for neural and/or neuropsychological compromise, regardless of the aetiological factors at play.

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