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SHORT REVIEW

Understanding the Neuropsychological Consequences of Deployment Stress: A Public Health Framework

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Abstract

Complaints of neuropsychological dysfunction have emerged among subsets of military personnel after almost every major deployment involving western nations in recent history. Although deployments have been characterized by a range of neural risk factors, psychological stress is common to most prolonged deployments. This review uses a public health framework to address associations between deployment-related stress and neuropsychological performance. Specifically, the review covers mechanisms by which deployment-related psychological stress may affect neuropsychological functioning, considers the advantages and disadvantages of approaching the question from a public health perspective, and discusses how epidemiological research may sort out questions regarding course, cause, and effect. (*JINS*, 2011, *17*, 1–6)

Keywords: Deployment, Stress, Neuropsychological functioning, Public health, Epidemiology, Veterans, Military personnel

INTRODUCTION

In the past decade, deployment has become increasingly common for U.S. service members but also affects military personnel worldwide. Although military deployment potentially provides benefits such as career-relevant experience and feelings of accomplishment (Maguen, Vogt, King, King, & Litz, 2006), deployment may also lead to adverse health outcomes, including neuropsychological dysfunction. After almost every major military engagement involving Western nations in recent history, subsets of returning military personnel have expressed neuropsychological complaints (Hyams, Wignall, & Roswell, 1996; Jones et al., 2002). Exposures possibly accounting for neuropsychological compromise include, but are not limited to, chemical warfare, traumatic brain injury (TBI), environmental pollutants (e.g., solvent-contaminated drinking water), occupational hazards (e.g., petroleum-based fuels, lead paint), physical stresses (e.g., extreme environments, prolonged sleep deprivation), and psychological stress.

This review focuses on relationships between deployment stress and neuropsychological performance. We recognize the influence of non–stress-related neural risk factors on post-deployment neuropsychological functioning but center on stress for two reasons. First, psychological stress is inherent to most major, prolonged military operational deployments, including both combat (King, King, Gudanowski, & Vreven, 1995; Nash, 2007) and non-combat (e.g., Bartone, Adler, & Vaitkus, 1998) deployments. Deployment may involve extended separations from family and friends, educational and occupational disruption, immersion in unfamiliar cultures and physically austere environments, physical injury, participation in dangerous duties, and exposures to environmental hazards, destruction, death, and the hardship of others. Second, animal and human cognitive neuroscience studies provide considerable evidence that exposure to stress may be linked to neurobehavioral performance.

We constrain this Short Review to a discussion of how public health methodologies may inform and be informed by cognitive neuroscience. Specifically, we articulate how deployment-related psychological stress may affect neuropsychological

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performance, discuss the advantages and disadvantages of approaching the question from a public health perspective, and discuss how epidemiological research may help sort out questions regarding course, cause, and effect.

WHY MIGHT DEPLOYMENT STRESS BE LINKED TO NEUROPSYCHOLOGICAL PERFORMANCE?

Stress And The Brain

Biological and psychological survival responses

From an evolutionary perspective, a rapid biological response to danger (e.g., an enemy combatant) is adaptive. Known as the "flight or fight" response, humans and many other species are "wired" to respond to danger with a series of physiological responses that allow actions that promote survival. In humans, the neural circuitry of fear is thought to involve several key frontal and limbic structures, including the prefrontal cortex (and in particular its medial, ventromedial, and orbital aspects), the amygdala, and the hippocampus (Shin & Liberzon, 2010). The animal literature has demonstrated that stress leads to activation of the limbic-hypothalamic-pituitary-adrenal (HPA) axis and neurotransmitter (e.g., noradrenergic and serontonergic), including those associated with arousal, that can result in neurobehavioral alterations (Arnsten, 2009; Morilak et al., 2005; Sauro, Jorgensen, & Pedlow, 2003). Such neurobiological activity is thought to alter the function and potentially even the structure of several brain regions mediating the stress response, including the amygdala, hippocampus, locus coeruleus, dorsal raphe nucleus, and prefrontal cortex (Southwick et al., 2007).

From a psychological perspective, neurobehavioral alterations in the context of duress may also promote survival by directing focus to potential sources of danger and away from irrelevant aspects of the environment. Because the ability to engage simultaneously in multiple focused cognitive activities is not unlimited, the diversion of cognitive resources to processing potential threat occurs at the expense of other cognitive activities (Constans, 2005).

Morgan and colleagues provided evidence of acute neurobiological (e.g., cortisol, neuropeptide-Y) and neurocognitive alterations (working memory and visuoconstruction) during survival training among military special forces members (Morgan, Doran, Steffian, Hazlett, & Southwick, 2006; Morgan et al., 2002). Although not a deployment, survival training is thought to represent realistically extreme military operational stress of the type that may be encountered during some deployments. In a prospective study of Army soldiers, Vasterling et al. (2006) found that military deployment to Iraq was associated with mild decrements in sustained attention, new learning, and memory, but deployment appeared beneficial to reaction time performance. These findings could not be explained solely on the basis of alcohol use, TBI, sleep, or emotional distress. Because returning service members were tested relatively recently (2 to 3 months) after their return from the warzone, we hypothesized that the subtle neuropsychological alterations displayed by returning veterans represented the remnants of an adaptive stress response carried forward from the warzone to home. A limited resource interpretation of the results suggests that gains in responding rapidly to designated targets (an advantageous survival skill in war) came at the expense of memory and sustained attention; not mutually exclusive, sustained activation of neurotransmitter (e.g., noradrenergic) systems associated with increased arousal that was initially adaptive in combat could also explain these findings. However, without corresponding experimental studies and/or quantification of stress exposure, such cognitive and biological interpretations, although conceptually appealing, can only be inferred.

Nontraumatic stress

Survival responses may not account fully for neuropsychological compromise associated with deployment stress. Proctor, Heaton, Dos Santos, Rosenman, and Heeren (2009), in a prospective study of National Guard soldiers, found that deployment to Bosnia for peacekeeping was also associated with pre- to post-deployment neuropsychological performance decrements in sustained attention and motor speed and improved performance on a working memory task. Consistent with findings indicating that mild stress can affect brain functioning in animals and that human cognitive performance may suffer as a function of social stress (Arnsten, 2009), The findings of Proctor et al. (2009) suggest that deployments without immediate life threat may also result in neuropsychological alterations. Contemporary returning veterans cohorts report significant homefront concerns while deployed, difficulties with transition to home life, and other non-life threatening stressful events in the war-zone in addition to those posing more imminent life threat (Street, Vogt, & Dutra, 2010; Vasterling et al., 2010). However, we currently know very little about which attributes of deployment other than frank neural insult drive observed neuropsychological alterations.

Chronic dysregulation

The chronic dysregulation of neurotransmitters and neuropeptides involved in stress responses is implicated in the etiology and maintenance of posttraumatic stress disorder (PTSD) and other stress-related psychiatric disorders (Yehuda, 2009a). In humans, structural and functional imaging has been used to examine neural abnormalities associated with stress-related psychiatric disorders. For example, functional imaging studies have suggested that PTSD is associated with exaggerated amygdala responses, deficient prefrontal function, and decreased hippocampal activation in response to symptom provocation and in cognitive activation paradigms (Garfinkel & Liberzon, 2009). Meta-analysis of

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structural MRI studies has likewise revealed that PTSD is associated with reduced hippocampal and anterior cingulate cortex volumes (Karl et al., 2006).

Emotional Sequelae of Stress Exposure as Potential Mediators

It is likely that associations between stress and postdeployment neuropsychological performance are partially mediated by emotional states. This may especially be true when emotional states reflect a chronic stress response. For example, although Vasterling et al. (2006) revealed deployment-related differences in neuropsychological functioning that were independent of emotional distress, PTSD and depression were also correlated with neuropsychological functioning in Iraq War returnees. In a cross-sectional study of 1991 Gulf War veterans, Toomey et al. (2009) found that depression symptoms and self-reported neurotoxicant exposures were independently and negatively correlated with sustained attention performance, one of two cognitive factors that differentiated a population-based sample of deployed versus non-deployed 1991 Gulf-War era veterans. David et al. (2002) likewise found that relative performance deficits on sequencing and attention tasks displayed by British 1991 Gulf War veterans with health complaints were accounted for by depression, although construction deficits remained after accounting for psychiatric symptoms.

Much of what is known about the stress response derives from animal studies, which permit examination of the acute effects of stress exposures on behavior. In humans, alterations in neuropsychological performance (most frequently seen in verbal learning and memory, working memory, sustained attention, and cognitive inhibitory functions) have in contrast typically been documented well after cessation of the initial psychological trauma exposure and appear more strongly associated with PTSD (e.g., Brewin, Kleiner, Vasterling, & Field, 2007). Comparing a smaller group of Iraq war veterans followed a year after their return from Iraq to a group assessed immediately after their return, Marx, Brailey et al. (2009) found that PTSD began to play a more dominant role in accounting for deficits in sustained attention with the passage of time, suggesting that the degree to which stress affects neuropsychological performance directly versus indirectly (i.e., through emotional distress) may in part depend on time since exposure.

Potential Interactions Between Physical and Psychological Insult

In the context of military deployment, stress may also involve extreme physical taxation or direct somatic insult. For example, WWII veterans held as prisoners of war (POWs) during their deployment described among the highest levels of psychological stress exposure reported among the WWII cohort, frequently endured torture involving head (and potential brain) injury, and for some, suffered extreme weight loss reflective of severe malnutrition. As compared to combat veterans who were not held as war prisoners, former POWs performed more poorly on neurocognitive tasks, with unique contributions made by physical stressors and stress-related psychological symptoms (Sutker, Vasterling, Brailey, & Allain, 1995). In reference to the 1991 Gulf War, questions have been raised about possible interactions between psychological stress and neurotoxic environmental exposures (Friedl, Grate, & Proctor, 2009; Friedman et al., 1996).

In the current military engagements in Iraq and Afghanistan, significant subsets of service members report exposure to blasts, accidents, and other events that are sometimes associated with TBI (Tanielian & Jaycox, 2008). Neuropsychological recovery from TBI may be complicated by concomitant psychological disorders (Lange, Iverson, & Rose, 2010). For example, in a sample of Iraq/Afghanistan veterans with TBI, Nelson, Yoash-Gantz, Pickett, and Campbell (2009) found that processing speed and color-word interference scores on a standard Stroop paradigm were more impaired in those with PTSD than those without PTSD, although this finding has not been universally replicated (c.f., Brenner et al., 2009). Likewise, psychiatric outcomes are poorer among psychological trauma survivors with brain injury (Bryant et al., 2010), particularly when associated with relative structural neuroimaging abnormalities in prefrontal and temporal regions (Mollica et al., 2009).

We view the exploration of synergies between non-psychological neural insult and psychologically driven neural alterations as having merit, avoiding potentially polarizing views focused on single etiologies that do not consider the complicated ways in which psychological stress and physical insults (e.g., TBI, environmental neurotoxicants) may interact.

Public Health Perspectives

Public health research often uses epidemiological methods, with the intent of generalizing findings to the population of concern. Public health studies, therefore, typically require larger samples constructed to represent broad subsets of the target population. One advantage of this approach is the ability to detect subtle population shifts that may be widely relevant. Even when modest in size for an individual participant, if negative health outcomes are sufficiently pervasive, functionally relevant, and potentially preventable or treatable, they hold significant implications for public policy.

Studies based on more heterogeneous populations without attention to at-risk subsamples, however, may fail to identify impaired subgroups because subgroup performances may be subsumed under the aggregated larger group. For example, a relative shortcoming of the Vasterling et al. (2006) report was that the relationship of deployment stress to neuropsychological performance was indirectly inferred on the basis that other risk factors commonly linked with neuropsychological compromise in military populations and/or deployment could not statistically account for associations between deployment

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and pre- to post-deployment neuropsychological change.[1] Ultimately, the goal of examining at-risk subsets or key variables influencing outcomes within a larger population is to identify factors that can be targeted for prevention or treatment interventions. The identification of protective factors is particularly relevant in light of recent attention to the constructs of psychological resiliency (defined alternately as the absence of psychological symptoms but, more commonly, as the ability to function well, even in the face of stress-related psychological symptoms) and psychological growth.

Finally, epidemiological studies often allow sensitivity analyses in which both exposures and outcomes can be examined within a full continuum, facilitating examination of dose and response more comprehensively. The occupational health and behavioral neurotoxicology literatures provide precedent for the application of a public health approach in the field of neuropsychology. Such studies have resulted in significant reforms in both occupational standards (e.g., organic solvents, lead) and public health policies (e.g., reducing lead in gasoline and paint, lower benzene levels in solvent mixtures). We see examination of deployment-related neuropsychological changes as another area ripe for such an approach.

As with any methodology, epidemiological methods come with trade-offs. As an example, sophisticated neuroimaging and electrophysiological methods have for a wide range of neuropsychological disorders helped elucidate the underlying neural mechanisms associated with performance deficits. These studies often use relatively small samples, comparing a disorder group to a comparison sample under conditions of tight experimental control. In contrast, many public health studies use field research methods, which collect data on large numbers of sometimes geographically dispersed participants in natural contexts rather than in laboratory or clinical settings. Thus, the application of certain types of technologically dependent methods have to date been cost-prohibitive and/or impractical. Similarly, more comprehensive neuropsychological batteries and experimental paradigms are not always feasible in epidemiological contexts due to time constraints and/or limited control of the environment (e.g., sound and light proofing). Thus, conduct of both public health research and more traditional clinical and laboratory-based studies is desirable.

Understanding Causal Relationships and Longitudinal Progression

Deployment stressors are by definition environmentally induced. However, much of the human literature linking PTSD and/or stress exposures to neuropsychological deficits is cross-sectional, thereby constraining directional inferences. The manipulation of extreme stress for experimental purposes poses obvious ethical challenges. Animal studies manipulating stressor exposure have been informative but do not generalize fully to the human experience of deployment. Similarly, human analogue studies can mimic some aspects of military deployment but cannot fully replicate actual deployments (especially those involving prolonged and/or multiple combat rotations). Likewise, cross-sectional research tells us little about changes in neuropsychological function over time or causal directions. We do not know with certainty whether neuropsychological compromise increases risk of stress-related psychological disorders following military deployment, is a consequence of deployment stress, or both.

An informative series of studies conducted on Vietnam combat veterans and their non–Vietnam-exposed identical twin brothers provided evidence that performance on intellectual, verbal memory, attention, executive, and configural processing tasks was more strongly related to familial factors than to combat exposure or PTSD (Gilbertson et al., 2006, 2007). Conversely, as compared to familial relationships, Vietnam-related PTSD in this cohort accounted more strongly for failure to retain extinction of learned fear (Milad et al., 2008). Correspondingly, there is evidence from twin research and biological paradigms that pre-trauma brain structure (Gilbertson et al., 2002) and glucocorticoid alterations (Yehuda, 2009b), respectively, may increase risk of developing PTSD following trauma exposure. Collectively, these studies suggest that some aspects of neuropsychological functioning may pre-dispose individuals to PTSD following trauma exposure, but that PTSD may alter certain aspects of fear-based learning.

Prospective research conducted on larger samples complements twin research in determining directional relationships between deployment, or between various consequences of deployment (e.g., PTSD), and neuropsychological functioning. Although lacking randomization, research including baseline and post-exposure assessments in at-risk populations can be thought of as "natural experiments," allowing comparison of outcome measures before and after the exposure and comparison of relevant subsets of the at-risk population. For example, using prospective methodology, Parslow and Jorm (2007) found that less proficient baseline performances on tasks of learning, memory retention, attention, working memory, and verbal intelligence were predictive of greater PTSD symptom severity following a large scale natural disaster. Marx, Doron-Lamarca et al. (2009) similarly found that pre-deployment visual memory performance was negatively correlated with post-deployment PTSD symptom severity, after accounting for combat intensity and baseline PTSD symptoms.

Even without baseline assessments or non-exposed comparison samples, longitudinal measurement allows examination of how health outcomes evolve over time and identification of factors that predict subsequent recovery versus chronic or escalating problems. For example, in the current military context, longitudinal research is well-suited to examine the impact of the repeated deployments on neuropsychological functioning. Repeated deployments hold particular relevance to stress sensitization, which refers to increases in neurobiological responsivity that build with

[1] Accordingly, we are in the process of completing secondary data analysis examining associations between stressor characteristics and neuropsychological outcomes, with preliminary findings indicating links between specific stressor characteristics and neuropsychological outcomes.

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subsequent stress exposures (Southwick et al., 2007). This may lead to a cumulative toll on neurobiological systems (and associated neuropsychological functions) when there is not sufficient time to recover between exposures, as may be the case with multiple deployments.

Finally, longitudinal cohort studies may prove fruitful in addressing gene × environment interactions. Recent research has identified neural, genetic, and epigenetic factors that influence the functioning of neural fear circuits and behaviors associated with successful coping (Feder, Nestler, & Charney, 2009). Although advances in the field of molecular genetics continue to develop at a rapid pace, most molecular genetic studies require extremely large sample sizes, particularly if trying to examine more than restricted candidate alleles (Bearden, Jasinska, & Freimer, 2009). Thus, use of large epidemiological samples to map prospectively assessed neuropsychological performance as a phenotype to biologically derived genetic information permits examination of gene × environment interactions in determining both short- and long-term neuropsychological outcomes of deployment stress, including risk for more significant later-life neuropsychological compromise. Of course, the value of any longitudinal approach will be limited by the extent to which phenotypic measures (including neuropsychological tests) are reliable indicators of change.

SUMMARY AND CONCLUSIONS

Animal and human analogue studies have provided strong evidence that laboratory stress is linked to brain dysfunction, but are limited in the extent to which we can extrapolate to military deployments. We likewise have evidence from longitudinal studies that deployment is associated with subtle longitudinal alterations on performance-based neuropsychological tests (Proctor et al., 2009; Vasterling et al., 2006) but can only infer indirectly that stress is a relevant causal factor. We suggest that a synthesis of these approaches may help refine knowledge regarding deployment stress and neuropsychological functioning.

We view several questions regarding the relationship of deployment-related stress to neuropsychological functioning as having particular potential to inform public policy and being well-suited to a blended public health/cognitive neuroscience approach: (1) Which, if any, pre-deployment neuropsychological measures or other neural biomarkers help predict stress-related psychiatric outcomes (e.g., PTSD) following deployment?; (2) Are there synergistic effects on brain functioning between deployment-related stress and other environmental factors (e.g., TBI, environmental neurotoxicants)?; (3) What are the potential longer term trajectories of stress-related brain dysfunction following deployment?; (4) Which individual difference factors (e.g., genetic variance, neural integrity, psychosocial variables) interact with deployment stress to influence the post-deployment course of neuropsychological functioning over time?; (5) Do stress-related changes in neuropsychological performance following deployment have functional significance, as displayed by occupational impairment, social impairment, increased injury risk, or other compromises in quality of life?; (6) Can we identify cost-effective neural biomarkers (e.g., imaging, electrophysiological, or biological abnormalities) that will provide convergent evidence of stress-related neural alterations following military deployment; and, can neural biomarkers help predict resiliency *versus* dysfunction following deployment stress exposure? A public health perspective has much to offer in moving the field forward, especially when combined with complementary approaches that allow application of experimental methodologies, the application of advanced technologies, and examination of converging measures of neural functioning.

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