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The tasking for this study was to evaluate the potential for adversaries to exploit advances in Human Performance Modification, and thus create a threat to national security. In making this assessment, we were asked to evaluate long-term scenarios. We have thus considered the present state of the art in pharmaceutical intervention in cognition and in brain-computer interfaces, and considered how possible future developments might proceed and be used by adversaries.

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Contents

EXECUTIVE SUMMARY

The fields of neuroscience, psycho-pharmacology, and cognition are in rapid flux because new scientific tools have provided the capability to develop fundamental understanding of linkages among brain activity, electrical and chemical stimulation, and human behavior. Applications to human performance modification are being driven primarily by medical needs, e.g., "cognitive repair," and there are significant new technological developments in this area. As a result, there is popular excitement about, and thus commercial markets for possible applications in "cognitive enhancement." This area is certain to be investigated extensively over the next decade. Awareness of developments in cognitive performance enhancement, including cultural differences in adoption, will be important because these may affect the behavior and effectiveness of opposing military forces in both symmetric and asymmetric warfare. The findings and recommendations of our study fall under three categories, evaluation of military effectiveness, brain plasticity, and brain-computer interface as outlined below.

Evaluation of Military Effectiveness

Findings:

1. There already exists outstanding in-house (military) U.S. expertise in assessment of human factors. This internal expertise is essential for evaluating how developments in human performance might be used by adversaries. Extrapolation of civilian research to military scenarios cannot be relied upon to yield useful conclusions.

2. The most immediate human performance factor in military effectiveness is degradation of performance under stressful conditions, particularly sleep deprivation. If an opposing force had a significant sleep advantage, this would pose a serious threat. However, the technical likelihood of such a development is small at present.

3. Normal cultural assessments of the effects of human performance improvement are likely to lead to incorrect conclusions with regard to military effectiveness. Furthermore, the publicity and scientific literature regarding human performance enhancement can easily be misinterpreted, yielding incorrect conclusions about potential military applications.

4. A broad range of nutritional supplements advertised to have some performance-enhancing effect is reportedly often used by soldiers on their own initiative. The effects of such supplements are generally small and have high variability from person to person. Such effects are unlikely to find direct military utility. However, the unregulated supplement supply train does present a vulnerability to attack.

Recommendations:

1. Maintain a strong internal research activity, with concomitant personnel expertise, because this is crucial for evaluation of potential threats based on the activityof adversaries in human performance modification.

2. Monitor enemy activities in sleep research, and maintain close understanding of open source sleep research. Use in-house military research on the safety and effectiveness of newly developing drugs for ameliorating the effects of sleep deprivation, such as ampakines, as a baseline for evaluating potential activities of adversaries.

3. Develop a corps of trained analysts capable of evaluating technical developments in human performance modification. These analysts should be trained in assessing the meaning of statistical metrics, and also in assessing the experimental methods and results of the original scientific literature on which claims are based.

4. Mitigate potential attacks to the supplement supply by educating military personnel regarding the risks, developing awareness of the gray

market supply, and implementing a testing program for soldiers to use to verify that the supplements they have bought are safe.

Brain Plasticity

Findings:

1. Increasing scientific understanding of the mechanisms of brain plasticity has lead to the development of training regimens for permanently establishing new neural pathways, and thus new cognitive capabilities. Adversaries could use such scientifically designed training regime's to increase troop effectiveness or modify troop behavior and/or emotional responses.

2. New types of neuropharmaceuticals are being developed that more directly target synaptic firing, and thus impact brain plasticity far more effectively than existing drugs (e.g., modafinil, donepezil). When approved for use, these new drugs will certainly have extensive off-label use for improvement of memory and cognitive performance. These drugs may have the additional effect of weakening or overwriting existing memories. Depending on the ultimate performance of these drugs, adversaries might use them in training programs or field operations.

Recommendations:

1. The US should monitor the state of the art in training capabilities, and evaluate their impact in military scenarios. Specific actions should include:

   (a) Use neuroscience tools to evaluate training effectiveness in US Military programs, and thus develop quantitative understanding of the levels and types of changes possible.

(b) Develop information training activities adversaries.

(c) Develop information about popular/commercial activities in training and how these may differ in cultures of adversaries.

2. The US should closely monitor the uses and capabilities of the new classes of plasticity-enhancing neuropharmaceuticals that are under development. The prevalence and effectiveness of these drugs in off-label uses in the US will be a significant indicator of how they may be used by adversaries. The market for these drugs in foreign cultures should also be monitored.

Brian-Computer Interface

Findings:

1. The ability to pick up electrical signals from the brain externally using EEG is well documented and has important applications in improving the quality of life for tetraplegics. The technique is, however, slow (10s of bits of information transfer per minute) and subject to electromyographic noise due to physical movement even at the level of eye movements. The potential for field applications is not evident.

2. The ability to modify brain activity using external stimuli (transcranial magnetic stimulation or direct current stimulation) is also well documented, however the ability to predict or control the response remains phenomenological.

3. The use of motor-nerve signals has proven valuable in controlling prosthetics and in providing feedback for recovering function following strokes or brain trauma.

4. Neural implants involving connections through specific nerve bundles (e.g., ocular, optical) have shown dramatic results for ameliorating severe disabilities, however the level of improvement in all cases is well below the level of normal function.

5. Direct implants into the brain most often involve undifferentiated stimulation of a locality in the brain (rather than individual contacts to neurons or synapses), and for humans have been limited to intransigent medical conditions. The demonstrated level of behavior control (in animal studies) has involved simple stimuli that either simulate known physical (sensory) signals for specific actions, or provide a "rewarding impulse.

6. At present the primary threat potential for adversarial use of a Brain-Computer interface may arise in a feedback mode, in which a the interface provides a soldier with a simple signal or a pain/pleasure pulse in response to externally provided situational information. Longer term adversarial developments may include prosthetic applications providing specialized sensory input or mechanical output.

Recommendations:

1. The US should maintain awareness of medical advances in brain-computer interface, especially use in prosthetic devices, and monitor any developing non-medical applications closely. The US should monitor how such developments are proceeding in other cultures.

BRIEFINGS

Briefing Title	Briefer
Building Better Humans? Possibilities for Human Performance Modification	Lily Johnston
Investigation into the Strategic Effects of Emerging Technologies with a Focus on Human Performance Modification	Jenny Hayward and Kevin Dean Defence Systems Analysis Division Australian Department of Defence
Brain Plasticity, Transcranial Magnetic Stimulation and DC Brain Polarization	Eric M. Wassermann, M.D. Brain Stimulation Unit National Institute of Neurological Disorders and Stroke National Institutes of Health
Defense Applications of Emerging Neuroscience and Nutrition Technologies	Harris R. Lieberman, Ph.D. Military Nutrition Division U.S. Army Research Institute of Environmental Medicine (USARIEM)
Associative Learning in Humans Exposed to Acute Uncontrollable Stress: Delay Type Eye Blink Conditioning Before and After Survival School	Gary Hazlett Yale University, Robert Mitchell Center for RPOW Studies, and NIMH
Sleep Deprivation, Cognitive Performance, and Biomathematical Modeling	Hans P.A. Van Dongen, Sleep and Performance Research Center Washington State University, Spokane
Human Performance Modification, Context and Considerations	Adam Russell and Bartlett Bulkley Scitor Corporation
Short- and Long-Term Adaptation to Extreme Stress	Ann M. Rasmusson Yale University School of Medicine VA National Center for PTSD Clinical Neuroscience Division
Methods to Enhance Human Performance	Douglas Kalman Ph.D. Candidate, Nutritional and Exercise Biochemistry Touro University
Three Paths to Cognitive Enhancement	Gary Lynch Department of Psychiatry University of California, Irvine
Policy Implications of Cognitive Enhancement Technologies	Thomas H. Karas Advanced Concepts Group Sandia National Laboratories

1 INTRODUCTION

Historical instances of human performance modifying activities (e.g. East German Olympic athletes, amphetamine use during WWII, effects of the use of khat in Somalia on US operations) are well known. In contrast, little is known about the present activities of adversaries in using/developing human performance modifiers. However, it is reasonable to assume that performance-modification tactics will at least be considered by adversaries. This possibility now should be considered with some seriousness, because of rapid advances in understanding brain function, in developing therapies for brain and spinal chord damage, and in psycho-pharmacology. The rapid developments in these areas have already raised serious ethical concerns about possible non-medical applications [1, 2]. In addition, popular imagination concerning the possible implications of developing technologies greatly outpaces the existing technical capabilities.

The tasking for this study was to evaluate the potential for adversaries to exploit advances in Human Performance Modification, and thus create a threat to national security. In making this assessment, we were asked to evaluate long-term scenarios. We have thus considered the present state of the art in pharmaceutical intervention in cognition and in brain-computer interfaces, and considered how possible future developments might proceed and be used by adversaries.

1.1 US Cultural Beliefs and HPM in the Military

Advances in technology, in particular in greatly enhanced situation awareness and information collection and transmission, have transformed the modern battlefield. The complexity of combat has increased, and with it the tempo of operations. This has created a greater need to make rapid tactical

decisions at lower command levels, and has thereby spread the responsibility for making leadership decisions to more personnel. This ongoing so-called Revolution in Military Affairs has long been addressed by serious U.S. military efforts to improve training, as for instance represented in the annual Interservice/Industry Training, Simulation and Education Conference [3], and the work presented there. The possibility that advances in neuroscience may lead to improved training methods is now a rapidly developing area of investigation, as in DARPA's Training and Human Effectiveness thrust [4]. However, the advances of neuroscience have also led to popular speculation about modifying human performance in ways that extend beyond the present norms of training. From a military perspective, the goal would be to improve the capability of military personnel to meet the many challenges of today's, and anticipated, battlefields, and thereby to gain a measure of mastery over their opponents. This report analyzes some approaches that have been suggested for optimizing individual performance, in the context of potential actions of an adversary who may not be guided by the same cultural or ethical concerns that govern US military operations. The measures considered include medical supplements; non-invasive modifications of brain effectiveness, for example by training and sleep optimization; neuro-pharmacology; and neural implants. In pursuing understanding on this subject one needs to measure the value of the proposed behavioral changes or medical actions relative to what can be gained by organizing and training our military to utilize the unique characteristics, and strengths, of American society and culture, that emphasize individual choice.

There can be no doubt that equipment, training and motivation are major contributors to force effectiveness. An important technical edge can be gained with accurate fire power at all levels of intensity; with advanced sensors covering the broadest possible range, from low to high intensities, and linked in an accurate and timely communication system to provide enhanced situational awareness; and with reliable intelligence enabling us to field operational systems for denying or degrading enemy sensors. Effective training is

required to insure good physical conditioning and respect for discipline. War games and statistically significant simulations are valuable tools in preparing soldiers for making quick and appropriate decisions in response to a wide variety of rapidly changing battlefield conditions. Motivation depends on reaffirming the individual soldiers' beliefs that they are risking their lives for important missions that they truly believe in.

With its strong scientific and technical base, America can provide its troops with the best equipment. However in assessing the potential advantages resulting from our technological edge, we have to recognize two realities:

1. Looking ahead over the next few decades, we are most likely to be engaged in asymmetric warfare scenarios involving surprises, and relatively primitive hit-and-run tactics, including suicidal attackers whose actions effectively neutralize much of our technological edge, IEDs and EFPs being two current examples.

2. In facing opponents with access to the most advanced technologies, we must anticipate that many, though not all, of our technical advantages will be fleeting, and effectively countered by the enemy's adaptive tactics.

These circumstances put a high premium on our ability to train and organize our military to master and fully exploit all their available tools, and to develop the skills for managing a rapidly changing and fluid battlefield decisively and with timely actions. The American culture and society can, and should, provide a significant advantage on this score if properly exploited in our military training and command structure. Young men and women growing up in our decentralized democratic society–with all its warts, problems, and room for improvement–have abundant opportunities to pattern their lives as individuals. They are naturally enabled and encouraged to make their own decisions as to how to meet challenges and make choices, generally with considerably less regimentation and with broader opportuni-

ties than in more centrally directed societies, particularly the autocratic or repressive ones. And it is just this experience in making important decisions when facing new opportunities and challenges that is increasingly needed on the modern battlefield. It is an advantage to be nourished, just as active participation in the democratic process and identification with the nation's policy goals can strengthen individuals' motivation. One can find strains of this theme in military histories going back to the 5th century BC, most eloquently in Pericles' famous Funeral Oration for the Athenian soldiers at the end of the first year of the Peloponnesian war. In more recent times, General Gerhard von Scharnhorst, of the German general staff, has written on this subject. His views are discussed extensively by Lt. Col. Arthur J. Corbett [5], based on the historical analysis of White [6], as exemplified by the following two quotes:

> "Enhancements in battlefield morale, initiative, leadership, operational mobility, and flexible tactical doctrine were among the many by-products of the (French) revolution discerned by Prussian military thinkers. Since the origins of these enhanced military capabilities were found in social institutions, they were overlooked in the first glance of traditional military theorists. Indeed, most Prussian officers accepted the existing social, political, economic, and military structures of Prussian society and refused to consider nonmilitary factors in their operational analysis. Scharnhorst saw this ignorance of French national character as the major reason for the Allied (sic) defeat"....
>
> "Scharnhorst was convinced that French military superiority was the direct result of a new French social and political order and the most significant sign of the changes was the greatly enhanced capability of the common French soldier and junior officer to exploit his natural intelligence and independent judgment"

It is difficult, if not impossible, to come up with metrics to measure the importance of the social and cultural factors, appropriately incorporated in training and military doctrine and organization [7], relative to measures such as behavioral changes and medical actions that might be used for achieving an edge in military effectiveness. However their importance is apparent. It will be instructive to see what can be learned about the effectiveness of various approaches to modifying human performance by studying their adoption in civilian capacities that make comparable demands on personnel in terms of intense pressure and the need for timely decisions with major consequences. Perhaps the closest comparison to turn to is medical training of interns who face life and death decisions in emergency room situations. Establishing a long-term evaluation of both policy and practice for medical interns could well be a fruitful task to undertake.

1.2 New Potential due to Advances in Neuroscience

Many years of effort in understanding the basic biochemical mechanisms of brain function, in combination with powerful new tools for imaging the brain, have come to fruition with direct consequences for medical practice [8] – [12]. The brain imaging tools, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), in combination with electroencephalograms (EEGs) provide powerful combinations of both spatially and temporally resolved information on brain function. These techniques are non-invasive and can be used on fully conscious subjects, allowing tests to correlate brain response, with human activities, with effects of pharmaceuticals and with effects of electromagnetic brain stimulation.

As a result, there have been rapid advances in areas of medical intervention for stroke recovery, spinal cord repair, development of prosthsetics and neural interfaces for tetraplegics. In the realm of psychiatric medicine, there have been developments of psychopmaraceuticals and brain stimula-

tion for treatment of serious illnesses such as post-traumatic stress disorder, depression, Alzheimer's disease and Parkinson's disease. In behavior and cognition, there have been advances in understanding the brain-basis for human responses, mechanisms of cognition, and the design of effective training approaches.

The humanitarian desire to ameliorate the effects of serious illness and disability is a strong motivation for this work. However, there are always concerns about the ethics of patient treatment, and the possibilities of spill-over of such efforts into commercially driven activities with potential for abuse. At present, the latter category remains largely hypothetical in technical feasibility, but looms large in popular imagination.

Non-medical applications of the advances of neuroscience research and medical technology also pose the potential for use by adversaries. In this context, we must consider the possibility that uses that we would consider unacceptable could be developed or applied either by a state-adversary, or by less-easily identified terrorist groups. In the following, we consider first the issues of what types of human performance modification might alter a military balance, and how those issues can be evaluated. We then address two broad areas where there are significant, and highly publicized, advances in human performance modification. These are the areas of brain plasticity (permanently changing the function of an individual's brain, either by training or by pharmaceuticals), and the area of brain-computer interface (augmenting normal performance via an external device directly linked to the nervous system). The present status of technology in these areas is evaluated, and the context for potential threats in the future is described. As will be seen, there are no serious immediate threats, however the advance of technology and the accompanying commercial interest, are such that close attention must be paid to the future potential for threats.

2 MILITARY UTILITY

To address the question of how adversaries might employ human performance modification to increase their military advantage, it is necessary to understand not only what modifications are possible, but also how human performance factors will impact real military situations. The latter is an issue of substantial military importance, and as a result the US military carries out significant research on the environmental factors that influence performance, including situational stresses, sleep, nutrition, training, and medical interventions [13, 14]. The resulting information and expertise concerning human performance under military conditions is essential to any analysis of how adversaries might use human performance enhancement in a military situation.

An important aspect of research in human performance is establishing routine and unbiased metrics, e.g., ways of measuring human performance, that can further be related to functional military activities [15]. An example of the correlation of diagnostic tests with functional performance is shown in Figure 2.1. The specific study involved tests of the effects of caffeine on performance for a group of Navy SEALS, following 72 hours of intense training activity with almost total sleep deprivation. A variety of metrics were used, including computer-based tests of reaction speed and mental acuity, psychiatric self-assessment surveys, and marksmanship tests. The test was to determine the optimal caffeine dose to ameliorate the effects of fatigue and stress. The results shown in Figure 2.1 reveal substantial improvements in many categories, although it should be noted that the improvements are defined relative to the performance level after 72 hours, which was seriously degraded in all cases relative to measurements taken before training.[1] However, despite the substantial improvements in some of the tests of mental acuity, marksmanship was only slightly improved. This shows that general

[1]For instance the percentage of missed targets increased from $\sim$ 3% for well-rested troops, to about 35% after 72 hours of high-stress training.

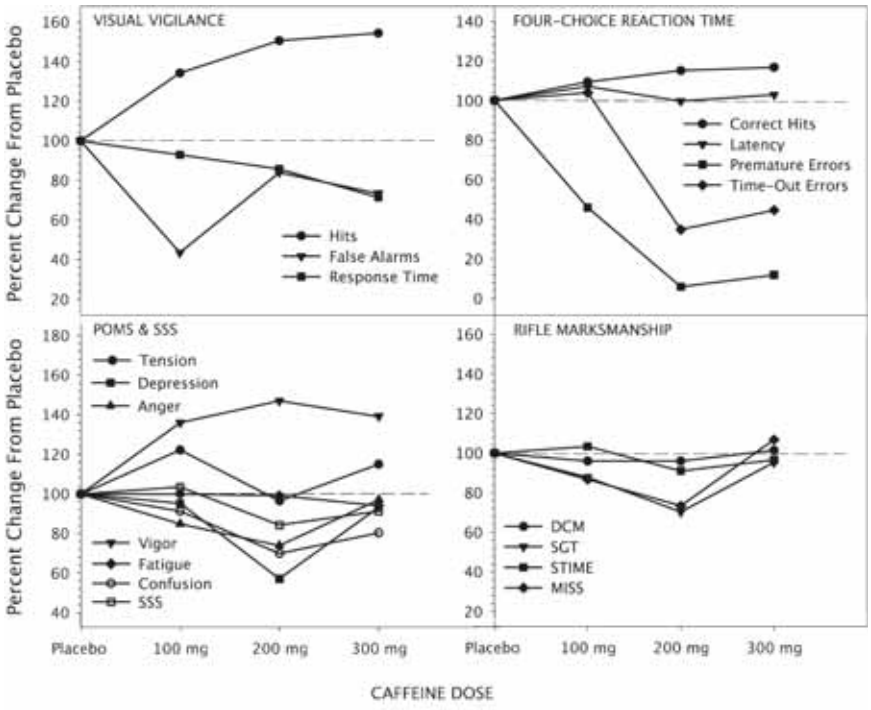

Figure 2.1: Performance indicators measured for 68 soldiers, who were divided into 4 groups, with members of each group administered the indicated doses of caffeine. The visual vigilance and four-choice reaction time tests involved computer-based activities. The POMS & SSS tests involved answering a series of questions concerning self-perception of mood and condition, and the rifle marksmanship tests measured the distance from the center (DCM), shot group tightness (SGT), number of missed targets (MISS) and sighting time (STIME). Results are normalized to measurements immediately before the caffeine doses were administered. From reference [16].

performance metrics, while useful for assessing overall personnel status, cannot be simply extrapolated to predict performance levels for specific military tasks.

Correctly interpreting how any modifications of human performance may affect military activities is essential to understanding the impact of potential adversarial actions. However, our ability to understand the military impact is complicated by cultural biases, misunderstanding of statistical information, and the human propensity to uncritically accept "good news" information. In the following sections, we will first use a standard simpli-

fied model of military effectiveness, the Lanchester model, to illustrate how our cultural biases can lead to incorrect conclusions about the impact of small performance gains on military success. We will then extend this model to show how issues of sleep deprivation, one of the most serious issues in military human performance, can be related quantitatively to military success. In Section 2.3, we show how common misunderstanding of statistical information often leads to incorrect conclusions, and illustrate the issue of "optimistic" interpretation of scientific results. Finally we discuss the issues of herbal remedies and supplements in the context of adversarial threat potential. A key finding of this section, that the US needs analysts trained in critically assessing technical information relative to human performance modification, is discussed in Section 2.5.

2.1 Force-on-Force Dynamics Is Different from Olympic Competition

We show here that the consequences of gaining a small performance advantage, even if it is highly statistically significant, are likely quite different as regards force-on-force engagements than as regards Olympic competition. In brief, a small performance advantage in force-on-force should generally result in a *small* change in the outcome, while in Olympic competition it can result in a *large* change in the outcome. We will illustrate the general principle with highly simplified, but quantitative, models.

2.1.1 Lanchester's Law for Force-on-Force Engagements

Lanchester, in 1916 [17] wrote down a simple model for the dynamics of a force-on-force engagement between a blue force A and a red force B. Let A be A's numerical force strength (number of troops, e.g.) and B be B's numerical force strength. Let k_A be the effectiveness of A per unit force strength. That

is k_A parameterizes A's (hopefully) better equipment, training, situational awareness, and so forth. Correspondingly we have k_B for B's effectiveness.

Lanchester's key concept, which defines the set of circumstances in which the model is applicable, is that B's casualities are proportional to both the size and the effectiveness of A, while A's casualties are proportional to both the size and the effectiveness of B. This gives immediately coupled differential equations that describes the drawdown of each force in the engagement:

$$\begin{aligned} \frac{dA}{dt} &= -k_B B \\ \frac{dB}{dt} &= -k_A A \end{aligned} \tag{2-1}$$

Lanchester observed that these equations have a conservation law, namely that the difference of the squares of the force size (each times its effectiveness) is constant during the engagement, that is,

$$V \equiv k_A A^2 - k_B B^2 = \text{constant} \tag{2-2}$$

is the conserved quantity. Proof:

$$\frac{d(k_A A^2 - k_B B^2)}{dt} = 2\left(k_A A \frac{dA}{dt} - k_B B \frac{dB}{dt}\right) = 2\left(-k_A A k_B B + k_B B k_A A\right) = 0 \tag{2-3}$$

We can use Equation (2-2) for example to calculate A's casuality rate in the event that A prevails, that is, attrits B's strength down to zero. If subscript i and f refer to initial and final values, respectively ($B_f = 0$), then

$$k_A A_f^2 = k_A A_i^2 - k_B B_i^2 \tag{2-4}$$

which can be rewritten as

$$\begin{aligned} C_A \equiv 1 - \frac{A_f}{A_i} &= 1 - \sqrt{1 - \frac{k_B}{k_A}\frac{B_i^2}{A_i^2}} \\ &\approx \frac{1}{2}\frac{k_B}{k_A}\frac{B_i^2}{A_i^2} \end{aligned} \tag{2-5}$$

Here C_A is A's fractional casualties. The approximation shown is valid when this fraction is small.

Some centuries-old rules of thumb for force-on-force combat can be found in Equation (2-5). For example, it is widely taught that at least a 3:1 numerical advantage is required for A to prevail over B in the case that B is in a fortified fixed position. One sees in Equation (2-5) that this can be viewed as a statement about the relative effectiveness of forces in offensive versus defensive positions, that they differ by about an order of magnitude ($\sim 3^2$), in favor of the defense.

Also widely taught is that, for equal force effectivenesses, a numerical advantage of 3:1 will allow A to prevail over B definitively — wipe B out — while taking only acceptable casualities himself. Equation (2-5) shows that this rule of thumb corresponds to the acceptable casualty rate being $\sim 5\%$, reasonably the case in all but very recent wars in which the U.S. has been involved.

Relevant to our application here, Equation (2-5) shows that small fractional increases in A's force effectiveness k_A change A's casualty rate (or, for that matter, ability to prevail) only by a small amount. In fact, the change is only half as much as would be achieved by the same fractional change in A's force size:

$$\frac{\delta C_A}{C_A} \approx -\frac{\delta k_A}{k_A} - 2\frac{\delta A_i}{A_i} \tag{2-6}$$

This result is illustrated for a 5% change in $A's$ effectiveness in Figure 2.2. As an example that we will use below, while increasing A's effectiveness by $\sim 16\%$ does allow A to prevail with $\sim 16\%$ fewer casualities, the same decrease in casualties could be achieved by increasing A's force size by 8%.

Lanchester's law does not deny the utility of increased force effectiveness — in fact, it quantifies it. However, it shows why, in a situation where A intends to prevail at acceptable casualty rates, small changes in force effectiveness can never make decisive changes in the outcome or large changes in A's casualty rate.

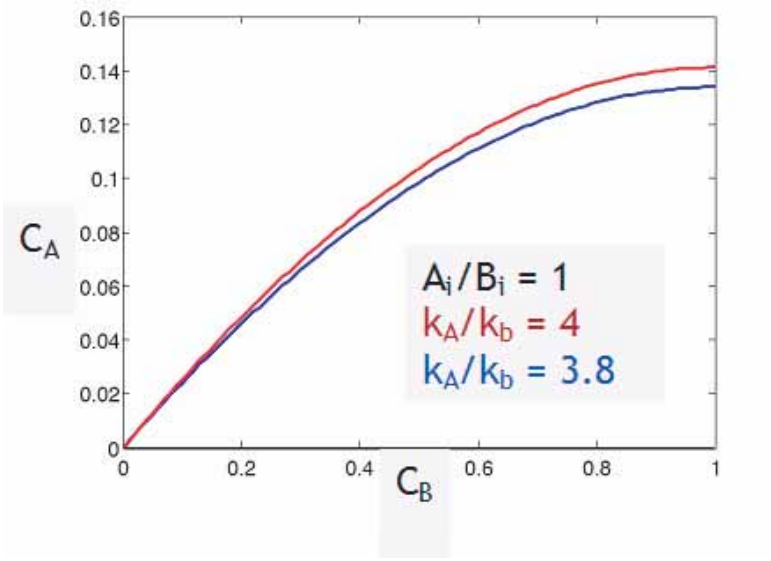

Figure 2.2: The evolution of the fractional casualties of the two forces is shown for the case where force A has a 4:1 advantage in effectiveness (red curve) and the force levels are initially matched ($Ai/Bi = 1$), yielding a limiting casualty rate (e.g. where force B takes 100% casualties) of 13.4%. A small change in the effectiveness rate (blue curve, effectiveness ratio decrease by 5% to 3.8), causes a proportionally small change in the evolution of the conflict in terms of relative casualties.

2.1.2 Olympic Competition

Why is our sense of things different for Olympic competition, where we widely believe that small changes in force effectiveness can make the difference between gold medalist and loser? The answer, in brief, is that, unlike force-on-force combat, Olympic competition takes place between players who are *all* many standard deviations out on the extreme favorable tail of a probability distribution defined by the general population.

As an idealized model, suppose that a country's Olympians are drawn from the extreme tail of a Gaussian (normal) probability distribution with selectivity S. That is, only one out of S in the eligible population (say, country residents between the ages of 16 and 25) can "make the team". Plausible values of S might be in the range 10^4 to 10^5. The number of

standard deviations t by which a typical Olympic team member exceeds the population mean in some performance variable (long jump distance, e.g.) is then related to the fraction of the population making the team $1/S$ by

$$\frac{1}{S} = \frac{1}{\sqrt{2\pi}} \int_t^\infty e^{-t'^2/2} dt' \approx \frac{1}{\sqrt{2\pi}t} e^{-t^2/2}. \tag{2-7}$$

For large S and $t >> 1$, an approximate inverse to this relationship is

$$t = \sqrt{4.6 \log_{10} S - 6.5}. \tag{2-8}$$

So $t \approx 3.5$ for $S = 10^4$, while $t \approx 4.1$ for $S = 10^5$.

Put differently, a performance increase of $4.1/3.5 - 1 = 17\%$ (as measured in standard deviations of a performance variable from the population mean) is the equivalent of a full factor of 10 greater selectivity S, from 10^4 to 10^5. This, roughly, is how a small country like the German Democratic Republic (DDR) was able, by the use of performance enhancing drugs, to produce Olympic teams competitive with countries that were an order of magnitude or more larger in population. On the tail of a distribution, small changes in your performance lead to large changes in how many people you are better than.

2.1.3 But Aren't the Special Forces Our Military Olympians?

Many U.S. Special Forces feel that they are the Olympian elite, and that the above logic of performance enhancement for Olympic athletes should apply to their situation. This is a false analogy.

In performing their missions, our elite special forces are rarely if ever competing symmetrically against opposition elite forces, with victory going to whichever side is farther out on the statistical tail of extreme performance. Rather, the situation described by Lanchester's law is much closer to the truth: A small, coherent (blue) special forces unit must "draw down to zero" a

generally larger number of (red) "obstacles". The obstacles may be opposing forces, or they may be performance challenges (climb the mountain, guess the opposition tactics, etc.). In turn, the obstacles are all capable of inflicting casualties on the blue unit. Red forces have some effective value $k_B B^2$ against which blue's $k_A A^2$ must successfully compete, generally by having a huge k_A effectiveness advantage. But as we have already seen, in the Lanchester model, no matter how large is k_A, it remains true that a small fractional change in k_A produces only a small additional advantage.

2.2 Sleep Deprivation

Sleep deprivation is known to have significantly harmful impact on physical performance, alertness, and the ability to perform complex cognitive tasks. In planning their campaigns, battlefield commanders have to weigh carefully the negative impact on the effectiveness of their forces of extended periods of wakefulness and combat. In addition, under appropriate conditions on the tactical battlefield, sleep deprivation and exhaustion can be and has been exploited militarily as a specific mechanism to weaken opposing forces.

This observation, most likely well recognized by senior commanders, is illustrated by accounts of General George Patton's almost legendary pattern of driving his army with extreme aggressiveness in World War II, based on his stated conviction that it was the way to reach his goal more rapidly and with fewer casualties. The point is to maximally exploit the state of exhaustion of ones enemy. It seems intuitive that, in combat between two armies at comparable levels of sleep deprivation, the advantage is with the force on offense in its ability to stress the opposition's state of exhaustion.

The deleterious effects of continuous sleep deprivation are well known. The effects of chronic sleep deprivation, more relevant to most military op-

erations, has been been studied quantitatively only recently [18], as shown in Figure 2.3. An effective field test, the psychomotor vigilance test (PVT), which is a demonstrated effective measure of the effects of sleep deprivation, was used to obtain the results shown. For 9 subjects who had eight hours of time in bed (TIB) per night, there was a 3-4 fold increase in the number of lapses over the 14 day period where the sleep restriction was mandated. For 13 subjects only allowed to have 6 (4) hours of TIB per night, the number of lapses increased 11 (16) fold.

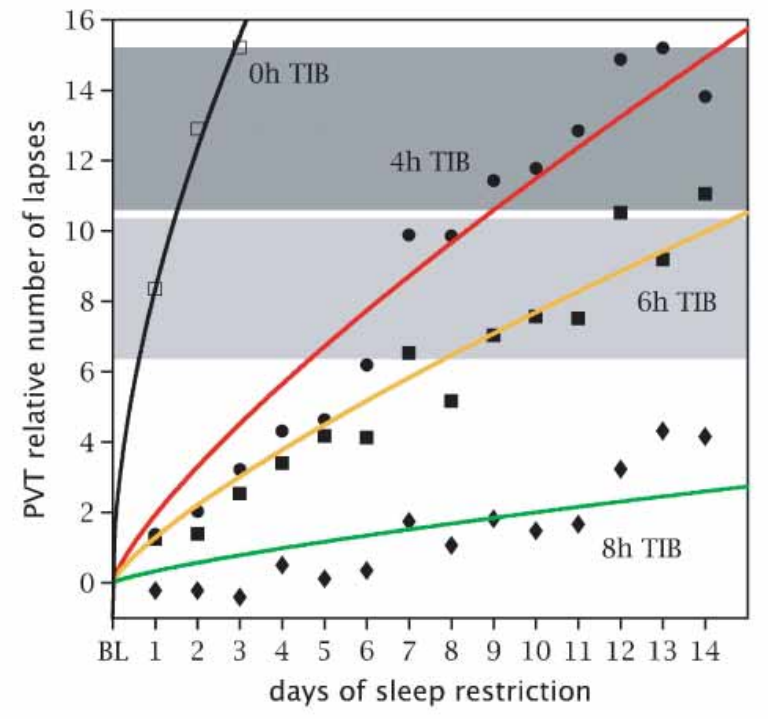

Figure 2.3:

These effects also exhibit dramatic consequences in combat situations. Lieberman and coworkers studied soldiers in U.S. Army elite units during a combat simulation field exercise [19]. Wrist activity monitors showed that the solidiers slept about 3 hours per night over a 53 hour period. Twenty four hours after their initial deployment they displayed significant decrements in their cognitive function, including vigilance, memory, reaction time and reasoning. The observed decrement in ability was several-fold worse than

individuals whose blood alcohol levels are above the legal limit. Although the combat exercise resulted in multiple stresses in addition to sleep deprivation (e.g. dehydration), the predominant effect leading to the performance decrement was sleep deprivation.

2.2.1 The ability of humans to withstand sleep deprivation has large individual to individual variations

How uniform is the human response to sleep deprivation? A recent study by van Dongen and coworkers demonstrated that there are substantial differences in the abilities of individuals to withstand sleep deprivation. They studied 21 adults from 21 years old to 38 years old, divided into two groups. Each underwent 36 hours of sleep deprivation. One group slept 6 hours a night before the sleep deprivation, and the second group slept 12 hours a night before the deprivation. Every two hours during the sleep deprivation, the subjects were given a variety of neurobehavioral tests, ranging from vigilance tests, digit substitution tests, and critical tracking tests. The subjects demonstrated a substantial individual-to-individual variation in their response to the tests. For example the number of performance lapses to a vigilance test ranged from 10-120 over the 21 subjects after 24 hours of sleep deprivation. In general the magnitude of the interindividual variability was large relative even to the effect of being in the 6 hour sleep group relative to the 12 hour group.

2.2.2 Animals show wide variety in sleeping times

In thinking about whether it might be possible to manipulate-either genetically or pharmacologically—the amount of times humans need to sleep, it is of interest to ask whether human sleeping characteristics are shared by all mammals. Although sleep is required by all mammals, the amounts of sleep

differ widely. For example humans need, on average, about 8 hours of sleep a night. There are organisms that require more sleep: the brown bat requires 20 hours /night; the tiger 16 hours/night; the squirrel 15 hours/night; the lion 13.5 hours/night and the dog 10 hours per night. On the other side, there are a range of animals needing far less sleep, ranging from the giraffe at 2 hours/night; the horse at 3 hours/night; the cow at 4 hours/night and the gray seal at 6 hours/night.

There is also a significant variation in the amount of time a human needs to sleep as a function of age; this ranges from about 16 hours per night at birth, to about 5.5 hours at death ($\sim$ 80 years old).

2.2.3 Why do we need sleep: nobody knows.

The sources of these variations are currently unknown. This is in large part because there is still very little understanding of why sleep is necessary, and in particular what sleep accomplishes. While we do not know why we sleep, much more is known about what is accomplished when we do sleep. In particular, there is substantial evidence that during sleep memories are played back of learned events and memory is consolidated or implanted in many animals.[20] How this would be accomplished were we not to sleep is not known.

2.2.4 The military consequences of sleep deprivation

Despite the present limited technical understanding, we would like to emphasize that the manipulation and understanding of human sleep is one part of human performance modification where significant breakthroughs could have national security consequences. If we take as a given that soldiers on the battlefield will always need to undergo sleep deprivation, some-

times severe, and given that such sleep deprivation leads to large performance degradation, it follows that any method for improving how soldiers behave under sleep deprivation will have significant consequences for either our own forces or an adversary that learns to solve this problem.

To illustrate the military consequences of sleep deprivation, we return to Lancaster's force on force model introduced previously in this report. There it was demonstrated that the casualty rate of A is given by

$$C_A = \frac{1}{2}\frac{k_B}{k_A}\frac{B_i^2}{A_i^2}, \tag{2-1}$$

where $k_A(k_B)$ is the effectiveness of A(B) per unit force strength, and A_i (B_i) is the initial size of the force for $A(B)$. Sleep modifies this model in two ways: First if the force sleeps a fraction τ of a day, the effective force size is decreased by a factor $1-\tau$. Hence if initially A's force has N people each of whom sleeps a fraction τ of the day then $A_i = N(1-\tau)$.

The second effect of sleep is that, as discussed above, the effectiveness k_A decreases with decreasing sleep. If we take $k_A = k_A(\tau)$, then as $\tau \to 0$ $k_A \to 0$, whereas as $\tau \to 1$ the effectiveness reaches its maximum $k_A \to k_A^*$. As a rule of thumb, we can thus assume that k_A has the form

$$k_A(\tau) = k_A^* \tanh(\frac{\tau}{\tau_0}), \tag{2-2}$$

where τ_0 is the amount of sleep below which there is significant degradation in k_A.

Now, we can rewrite Equation (2-1) as

$$C_A = \frac{1}{2}\frac{k_B}{k_A^*}\frac{B_i^2}{N^2} g(\tau), \tag{2-3}$$

where

$$g(\tau) = \frac{1}{(1-\tau)^2 \tanh(\tau/\tau_0)}. \tag{2-4}$$

Through $g(\tau)$, the casualty rate is now a function of the amount of sleep τ; hence, there is an optimal $\tau = \tau^*$ where the casualty rate is minimized. The

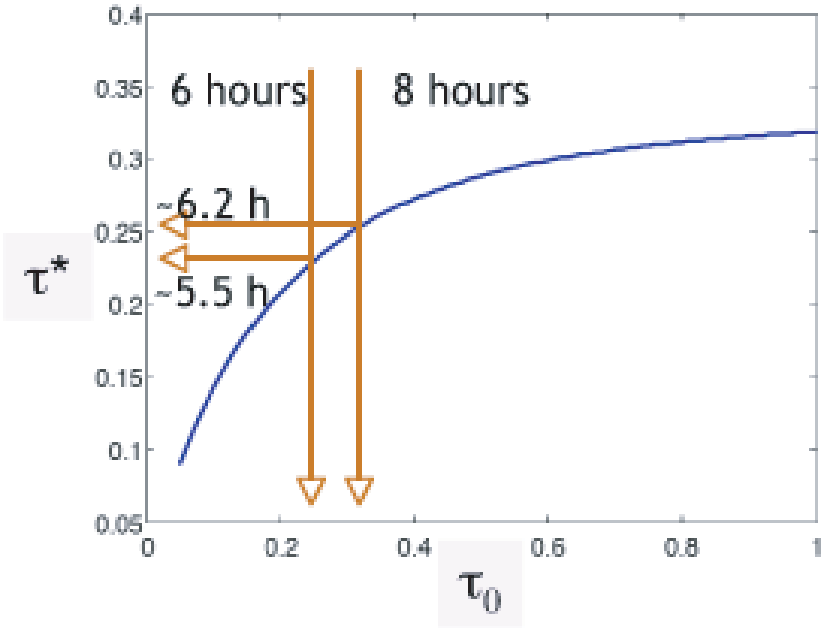

Figure 2.4: Optimal sleep time τ^* as a function of τ_0.

optimal amount of sleep τ^* solves the equation

$$\tau_0 \sinh(2\tau^*/\tau_0) = 1 - \tau^*. \tag{2-5}$$

Figure 2.4 shows the optimal sleep time τ^* as a function of τ_0: Note that the optimal time τ^* is a fairly weak function of τ_0. For $\tau_0 = 1/4$ or $1/3$ (corresponding to 6 and 8 hours of sleep per night, respectively) the optimal sleep times are $\tau^* = 0.23, 0.26$, respectively—corresponding to 5.5 and 6.2 hours of sleep per night. Hence in this simple model, the time that the soldiers should sleep is roughly independent of the time over which significant degradation of their abilities occurs.

On the other hand, there is a significant dependence of the casualty rate on τ_0. Figure 2.5 shows the casualty rate as a function of τ_0. The results are normalized relative to the casualty rate for $\tau_0 = 1/3$. This corresponds to 8 hours of sleep per night, which is roughly the amount of sleep needed each night to continue to score highly on a vigilance test over long periods. If τ_0 could be decreased to $1/4$ (corresponding to 6 hours of sleep per night) there would be a 23 % decrease in the casualty rate.

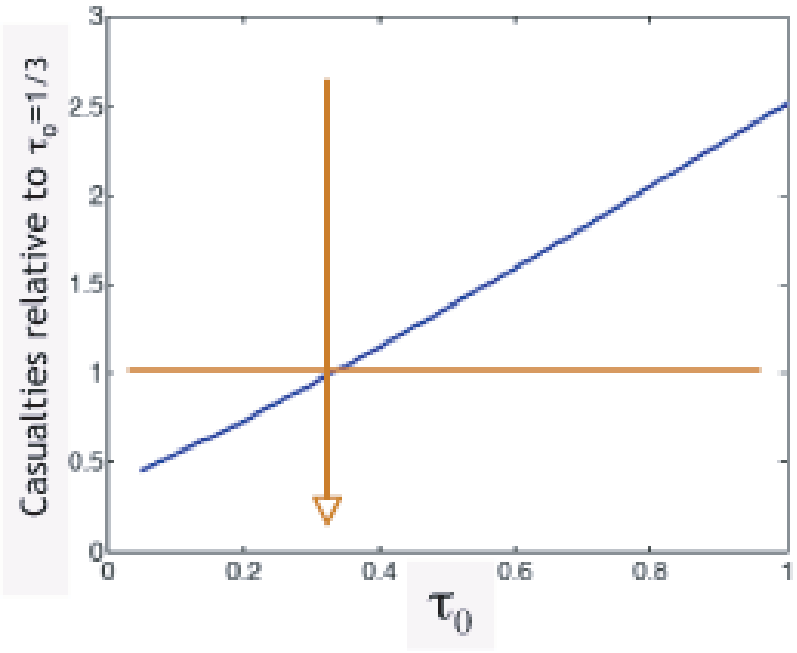

Figure 2.5: Casualty rate as a function of τ_0. The casualty rate is normalized to unity for $\tau_0 = 1/3$, corresponding to 8 hours of sleep per night.

It is worth noting that although the casualty rate is very sensitive to τ_0, it is much less sensitive to the amount of time a soldier sleeps at night. For example, if $\tau_0 = 1/3$, the minimum casualty rate occurs when the soldier sleeps 6.2 hours per night. If the soldier instead sleeps 5 hours per night (19% less than the optimum 6.2 hours), the increase in the casualty rate is only 2 percent. If the soldier sleeps 4 hours per night (35% less than the optimum), the casualty rate increases by 11 percent.

This model leads to several important conclusions:

1. There is an optimal amount of time that a soldier should sleep at night. This optimum is the result of the balance between troop size on one hand and skill degradation due to fatigue. The optimal time that the soldier should sleep depends only weakly on τ_0, the sleep time around which significant degradation in individual abilities occurs.

2. However, the maximum casualty rate depends strongly on the individual's sleep need, τ_0. Hence any effort to improve human performance to minimize τ_0 for given tasks can lead to a significant decrease in the casualty rate, of order 20 percent.

3. The casualty rate depends weakly on the amount of time that soldiers are allowed to sleep. Within this model if we assume that the soldiers need to sleep around 8 hours per night to maintain their skill levels, as long as they can sleep 5 hours per night there is not a significant increase in the casualty rate.

4. Suppose a human could be engineered who slept for the same amount of time as a giraffe (1.9 hours per night). This would lead to an approximately *twofold* decrease in the casualty rate. An adversary would need an approximately 40 percent increase in the troop level to compensate for this advantage.

2.3 Statistics and Analysis

There is a serious misunderstanding in general understanding of reports of "significance" in scientific results. To most non-scientists, the word "significant" is interpreted as "important and useful, whereas in scientific terms "significant" means only that an observed difference did not occur by chance. In clinical trials, sports training, and other aspects of human performance modification, effects are often reported popularly to be meritorious depending on whether they have been reported as statistically significant. However, despite the commonly encountered hyperbole, a report that something is highly statistically significant does not mean that the effect is necessarily large, or even important. We briefly review below the basics of statistical significance, to expand upon the above statements.

When used in conjunction with statistics, "significant" means solely that the result, within some stated probability, is not likely due to chance. A commonly used level to indicate that a measured effect is believable is 0.95, indicting that the finding has a 95% chance of being true. In fact, the actual meaning of such a statement is that the result has only a five percent chance of not being true, i.e., of being due to random chance. The p-value (described below) is often used as a numerical indicator of the probability of a result not being true, i.e., of the result being statistically significant.

First one should determine the confidence limit. It is not possible to measure every sample in the population, so one must instead calculate a range within which the population value is likely to fall. "Likely" is usually taken to be "95% of the time", and the range is called the confidence interval. Another important concept embodied in confidence limits is precision of estimation. The wider the confidence interval, the less the precision.

If the confidence interval does not overlap zero, the effect is said to be statistically significant. The value for an observable corresponding to no effect in the population is called the null value. For correlations and for changes in the mean, the null value is zero. To estimate the p-value, one has to test the null hypothesis, in which one first assumes that there is no effect in the population. Then one determines if the value obtained for the effect in the sample is what one would expect for no effect in the population. If the value one gets is unlikely for no effect, one then concludes that there is an effect, and concludes that the result is "statistically significant".

For example, suppose one is interested in assessing if there is a correlation between height and weight on a sample of 20 human subjects. One first must assume no correlation in the population, and then estimate what "unlikely" means. In this case, one might estimate that perhaps 5% of the time a correlation would be observed between height and weight, if there were in fact not a true correlation. If one then observed that, for a 20 subject population, height and weight were positively correlated 50% of the time,

or even 20% of the time, one would conclude that the result is statistically significant. This conclusion, however, says nothing about the amplitude of the correlation, i.e., about how important the correlation actually is.

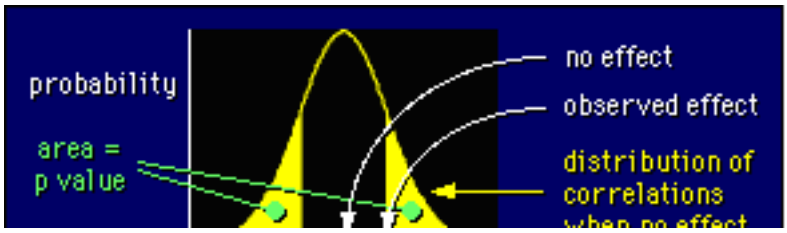

Figure 2.6: The p-value is a quantification of the statistical significance of the result. The p-value describes the probability of obtaining a result that is more extreme either positive or negative than the observed correlation. If the p value is less than 0.05 (5%), the correlation must be greater than the threshold value, so the result is concluded to be statistically significant.

Even if a result is statistically significant, that says nothing about its usefulness. For example, consider the distributions in Figure 2.7a. The means of the distributions in red, green and blue, respectively, are identical, yet the difference of red distribution with respect to the purple distribution is more statistically significant than that of the green distribution, which in turn is more significant than that of the blue distribution. However the change in the means relative to the purple distribution is the same for all three distributions.

Another example can be illustrated by considering the data in Figure 2.7b. These data are a scatter plot of 100 data points. The line indicates a correlation that explains just 4% of the variation in y (i.e., $r = 0.2$), but which is considered statistically significant, having a p-value of $p < 0.05$. This data set strikingly illustrates the difference, even to the uneducated observer, between a statistically significant correlation and an important one.

The p value provides a valid metric to describe the probability that the effect has *any* positive (or negative) value. If one observes a statistically significant, positive effect, then the true value of the effect is likely to be pos-

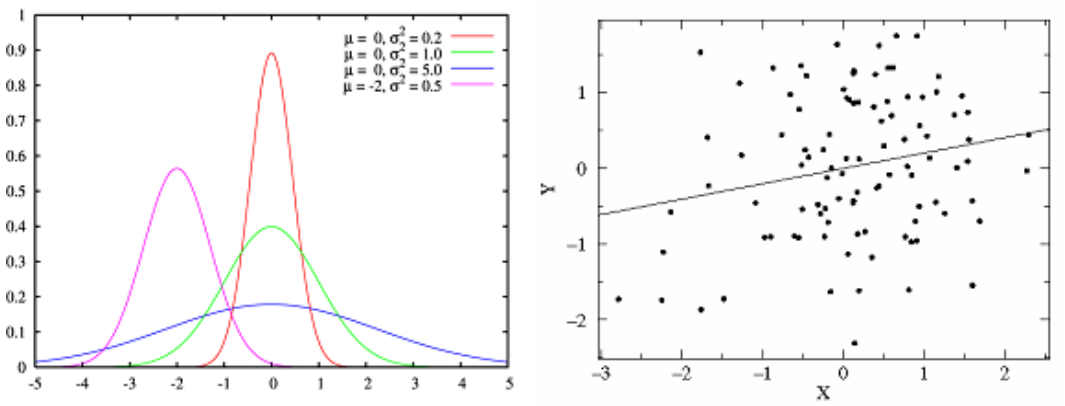

Figure 2.7: Model illustrations of statistically significance. Left (a), the width of a distribution is important in the evaluation of an observed difference in means. Right (b), a stastically significant correlation may be much smaller than the scatter in the data, rendering predictability based on the correlation impossible.

itive. However, as noted above, the determination that a result is statistically significant often does not correspond to the general understanding of "significance". In other words, for useful reporting (or interpretation of reporting) one wants to know the probability *of clinical or practical significance*. Those values rely on a determination of smallest clinically important positive and negative values of the effect; that is, the smallest values that matter to the subjects. It then is relatively simple to calculate the probability that the true value of the effect is greater than the positive value, and the probability that the true value is less than the negative value.

The smallest clinically important value is often called a threshold value for the chance of a clinically important effect. One thus has to choose a threshold value on the basis of experience or understanding. One also has to include the observed value of the statistic and the p-value. For changes or differences between means, one also has to provide the number of degrees of freedom for the effect (but the exact value is not crucial). Statistical analysis will then yield the chances (expressed as probabilities and odds) that the true value is clinically positive (greater than the smallest positive clinically important value), clinically negative (less than the negative of the smallest

important value), and clinically trivial (between the positive and negative smallest important values) (Figure 2.8).

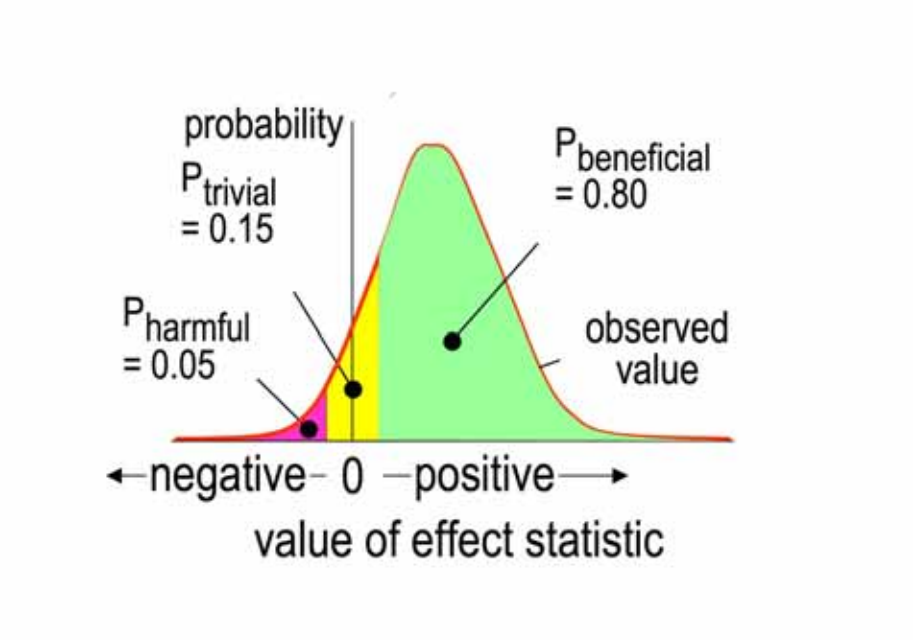

Figure 2.8: The smallest clinically beneficial and harmful values define probabilities that the true effect could be clinically beneficial, trivial, or harmful ($P_{beneficial}$, $P_{trivial}$, $P_{harmful}$).

Only convention establishes that a result with a p-value of, for example, 0.05 is statistically significant, as opposed to establishing the threshold for statistical significance at a p-value of 0.01. If one states that the level of significance is 5% (also called an alpha level), then any result with a p-value of less than 0.05 is statistically significant. In many journals, results in figures are marked with one asterisk if $p < 0.05$ and with two asterisks if $p < 0.01$.

Finally, we note the caution that should be taken when using correlations and average values to estimate the performance of highly selected, and highly trained, members of a population. For example, it is well-known that being obese, and being short, will adversely affect performance of an individual in the sport of basketball. Figure 2.9 shows that 31% of Americans are considered obese, whereas only 11% of residents of the Netherlands are obese. Furthermore the average male Netherlands resident is significantly taller, yet

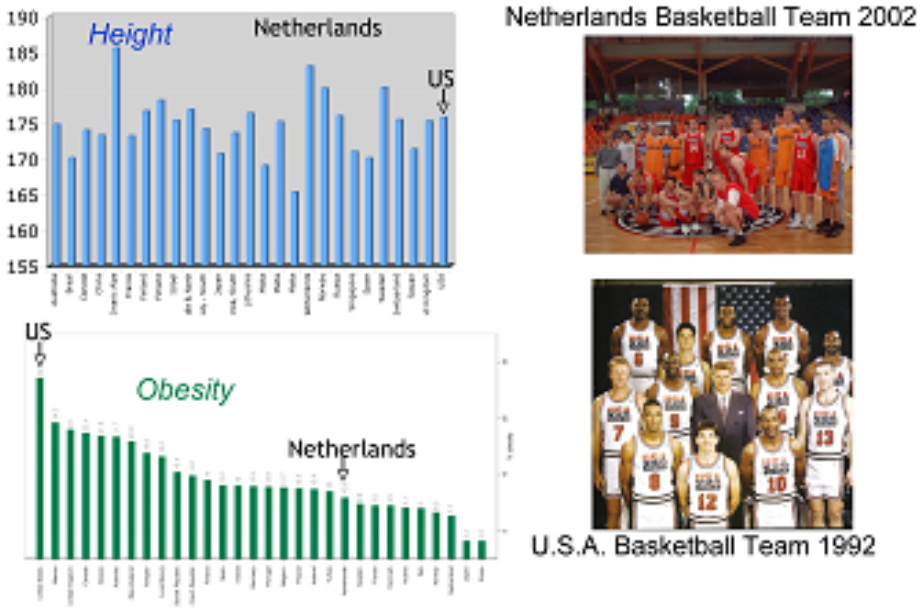

Figure 2.9: Population averages for height and weight do not provide enough information to predict the outcomes when sample selection occurs from populations of very different size. Larger populations allow much larger probabilities of finding an individual far from the norm.

it would be erroneous to conclude that the Netherlands Olympic basketball team would have a statistically significant advantage over the U.S. Olympic basketball team. The individuals on both teams clearly reflect a highly selected, highly trained cohort, which are not in any way described by the mean characteristics of the populations of large. Furthermore, there are significant differences in culture and training that are important in determining team performance. Therefore, it is not at all clear that a treatment that would increase further the average height of a male Netherlands resident, by say, 5%, would lead any time soon to a gold medal for the Netherlands Olympic mens basketball team, or would enable them to prevail in a statistically significant fashion in a series of games (or even in a single game) against the U.S. Olympic mens basketball team.

In the simple examples presented above, the statistical issues are easy to discern. However, in scientific presentations, the issues of significance are not always so easy to unravel. Clearly, one needs a cadre of well-trained analysts, who are versed in both statistical and critical analysis, to assess not only the statistical significance of scientific reports of purported human performance modification method, but also its clinical, general, and in our case, military importance, for the situations of concern.

2.4 Erogogenic and Cognitive Supplements

The use of supplements, primarily to ameliorate sleep deprivation and to improve physical performance, is report to be common among US military personnel [21]. This behavior is a cultural norm in the US and is recognized, but not endorsed, by the US military. For instance the PX at most military bases stock popular supplements. The use and efficacy of such supplements is highly variable. The US military, as part of the Technical Cooperation Program [22] with close allies (Canada, Great Britain, Australia, and New Zealand), has a long-standing effort in tracking and evaluating popular supplements. To date, 86 proposed ergogenic and cognitive aids have been evaluated, with a small number demonstrating sufficient activity to be potentially interesting. A sample entry, for the supplement tyrosine, is shown in Figure 2.10. For each entry, the panel assesses the scientific evidence and possible mechanism for activity, dosages, and potential side effects and health hazards. The example shown, tyrosine, is under continuing investigation because there is significant evidence for its activity.

While it is possible to improve athletic performance using supplements, or banned substances (e.g the former East German sports teams), such improvements often are either small in effect (see discussion in Section 2.1), highly variable from individual to individual, or dependent on coordination with highly disciplined training regimes. As a result, the tactical advantage

Tyrosine

Cognitive	Physical
Claimed benefits Improved cognitive performance during periods of acute psychological and/or intense environmental stress. Increased ability to resist stress.	**Claimed benefits** Aerobic capacity.
Effectiveness Equivocal, but there are many positive studies in the literature, including studies with military populations.	**Effectiveness** Unproven.
Mode of action Precursor of central and peripheral catecholaminergic neurotransmitters doapamine and norepinephrine.	**Mode of action** As for Cognitive Performance.
Duration of effect Estimated to be 4–6 hours, based on pharmacokinetics, but insufficient behavioral data are available.	**Duration of effect** As for Cognitive Performance.
Dose / time course & method of administration Many studies have administered 100 mg/kg taken in two 50 mg/kg doses over several hours.	**Dose / time course & method of administration** No information is available.
Chronic treatment Studies have reported no serious side-effects during long term therapy for depression.	**Chronic treatment** As for Cognitive Performance.

Hazards

Occasional gastrointestinal distress has been reported.

Other benefits

Cognitive performance: mood states during adverse exposures to cold and altitude are improved. This may lead to a physical performance improvement.

Comments

Tyrosine has been reported to enhance mental performance, improve mood and memory, and diminish symptoms in human participants exposed to such stressors as cold, high altitude and psychological stress. Indirectly it thus may enhance performance. Its ratio with other large neutral amino acids—leucine, isoleucine, and valine—is important. Its effect is blocked if given with these other amino acids. It may also have value in treating stress response to severe exercise. Tyrosine has been shown to be effective in rats. Cognitive performance improvements in humans have also been reported. Physical performance effects are relatively insignificant. Tyrosine may have potential value for cognitive performance. May have beneficial application when working in cold water. It is a candidate for further research.

Summary judgement

Physical: No known direct ergogenic benefit, but may indirectly enhance performance via cognitive or perceptual mechanisms.
Cognitive: Not proven to be effective but may be useful during periods of severe, acute environmental or psychological stress.

Figure 2.10: Entry for the supplement, tyrosine, from the 4th edition of the TTCP analysis of ergogenic and cognitive aids, reference [21].

that might be gained by any adversary employing supplements is not likely to be overwhelming in general operations. Special circumstances, as in the use of khat in Somalia, can however contribute to unexpected enemy behavior. Therefore it is important for the US to establish and maintain awareness of adversaries' uses of performance modifying substances (either as part of local culture, or officially established military policy).

2.4.1 Adulteration Threat

Self-medication is pervasive in American culture. As shown in Table1, in addition to the well-recognized illegal drugs, there is extensive misuse of prescription drugs, with more than 50% of the misused drugs obtained from the prescribed drugs of friends or relatives [23]. Given extensive willingness to experiment with unauthorized uses of prescription drugs, it is not surprising that young adults are also open to experimentation with legally obtained nutritional supplements, especially those advertised for enhancement of athletic performance. A 2003 U.S. Army Research Institute Study on non-prescription supplement use among Special Forces during the year 2000 showed that 90% of Special Forces soldiers and 76% of support soldiers used supplements. The most common supplements were energy boosters, vitamins, protein powders, and creatine.

While nutritional supplements are available to military personnel at the military PX, in conflicts where the force is in-country for an extended time, local markets also develop. These local markets will attract customers by offering lower prices, and may also offer supplements that fall outside of U.S. regulatory restrictions. In addition to simple health risks due to poor controls over the quality and dosing of these locally-supplied supplements, it is possible that such markets could serve as a method of intentionally poisoning U.S. personnel. This could be accomplished by the addition of slow-acting toxic chemicals, some of which can be obtained and used with

Table 1: Frequency in percent of different types of non-medical drug use among persons aged 18 to 25, correlated with cigarette use, for years 2005 and 2006.

Drug	CIGARETTE USE IN PAST MONTH			
	Any Use		No Use	
	2005	2006	2005	2006
ILLICIT DRUGS[1]	36.0	37.1	10.0[a]	9.0
Marijuana and Hashish	30.7	31.6	7.5[a]	6.7
Cocaine	5.5	4.9	0.7	0.6
Crack	0.7	0.5	0.1	0.0
Heroin	0.4	0.4	0.0	0.0
Hallucinogens	2.9	3.5	0.7	0.6
LSD	0.3	0.4	0.1	0.1
PCP	0.1	0.1	*	0.0
Ecstasy	1.6	2.1	0.3	0.3
Inhalants	0.8	0.7	0.2	0.2
Nonmedical Use of Psychotherapeutics[2]	11.2	12.0	3.1	2.9
Pain Relievers	8.5	9.4	2.3	2.1
OxyContin®	1.0	1.1	0.1[a]	0.0
Tranquilizers	3.6	4.1	0.8	0.7
Stimulants	2.6	2.6	0.5	0.4
Sedatives	0.4	0.3	0.1	0.1
ILLICIT DRUGS OTHER THAN MARIJUANA[1]	16.1	17.1	4.1	3.8

*Low precision, no estimate reported.
[a] Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.
[b] Difference between estimate and 2006 estimate is statistically significant at the 0.01 level.
[1] Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. Illicit Drugs Other Than Marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.
[2] Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives and does not include over-the-counter drugs.
Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2005 and 2006.

little technological expertise. An illustrative example is lead poisoning. Lead salts are easily obtained and could be mixed with nutritional supplements in a way that would be undetectable without special analytical procedures. Lead poisoning has a slow onset of symptoms that are easily misdiagnosed in the early stages. These symptoms include fatigue, irritability, and difficulty in concentration. At later stages the symptoms become more severe and include headache, abdominal pain, and joint pain, progressing to anemia and peripheral motor neuropathy.

The threat of intentional adulteration of nutritional supplements is quite plausible and well suited to the potential activity of small cells of terrorists or insurgents. Protective actions against such threats would include: 1) educat-

ing military personal regarding the (uncontrolled) risks and (limited) benefits of unauthorized supplies of supplements; 2) increasing official awareness and surveillance of gray-market supply chains for such materials; 3) implementing a testing program for military personnel that allows them to have supplement purchases evaluated for potential adulteration.

2.5 Summary

The human performance factor is an important component of the overall performance advantage of one military force with respect to another. However, it is difficult to assess how human performance factors will couple with the many other factors of military performance to affect the actual outcome of an engagement. In this context it is very important to avoid simplistic assumptions, such as "if the soldiers are 2% stronger, we will win 2% more engagements)", in analysis or policy decisions. We have used a simple model of military engagement (the Lanchester force-on-force model), to illustrate the fallacy of the assumption, based on analogy with sports doping, that small enhancements in performance would cause dramatic changes in the balance of military result. The same model also was used to illustrate the dramatic effects that a *major* change in human performance, namely a decrease in the need for sleep, could have on the balance of military effectiveness. The use of the Lanchester model illustrates the qualitative understanding that can result from evaluating military contexts. Variants of the Lanchester model, for instance for asymmetric warfare [24], are also known, and can also be used for similar analyses. One strong recommendation of this report is that analysis of military threats that might arise from adversarial use of human performance modification be placed in a realistic context of military effectiveness.

There is also reason for a serious concern about public perceptions of medical advances, and misunderstanding of the scientific literature in assess-

ing the effectiveness of human performance modification. We have presented a discussion of the types of incorrect conclusions that can result, for instance due to the mismatch between the normal and statistical meanings of "significance." A second strong recommendation of this report is that analysts involved in analysis of advances in human performance modification have (or be given) a strong enough technical training to be able to evaluate reports critically, including technical critiques of the originating scientific reports.

Finally we have addressed the issue of popular use of supplements. (Issues of regulated pharmaceuticals, including off-label prescription drug use, will be addressed in the following section.) The use of supplements in the US, both in the civilian and military populations, is widespread. There are certainly supplements that have ergogenic or cognitive effects, however their adaptation to developing a major military advantage is unlikely because of one or more of the following limitations: small absolute effect, high variability in effect from individual to individual, and/or strong dependence of effect on correlated rigorous training. A third recommendation of this report is that the US maintain awareness of popular supplements, and extend that awareness to behavior in adveraries' cultures. In addition, there also is a potential threat to US operations that could arise due to adulteration of the supplement supply train to US military forces.

3 BRAIN PLASTICITY

The entire concept of human performance modification is undergoing major changes as a result of advances in understanding how the brain works. Most important is the area of brain plasticity, that is the physiological changes in the brain that result from learning and adaptation. Scientific understanding of how these changes occur is paralleled with understanding of methods, including both training and pharmacological intervention, of how these changes can be induced. At present, there is clear evidence that interventions based on brain plasticity can repair deficits resulting from disease, degeneration, environmental stress, trauma and psychiatric problems. There is also great interest in the possibility of enhancing normal human function. However, there is little evidence as yet concerning whether the latter is actually achievable.

In the following we will first address the review the neurological basis of brain plasticity, that is, the biochemical processes that are involved in transmitting a signal between neurons (across the synaptic junctions between the neural dendrites). This review only includes the minimal information needed to illustrate the mechanisms: we will present only a summary of a single type of neurotransmitter, and will not discuss the complex regulatory and feedback biochemical networks that are coupled to the action of this neurotransmitter. We will then present some examples of brain plasticity resulting from carefully designed training regimes. The issues of pharmacological intervention will then be addressed, especially a new class of drugs that directly target the neurotransmitters in a way that can dramatically affect brain plasticity. We will conclude by discussing the threats that might arise due to an adversary's exploitation of brain plasticity.

3.1 Cellular Mechanisms Underlying Memory and Learning

The network connections among neurons can be modified by intercellular electrical signaling activity that induces intracellular chemical processes in the receiving cell. These connections can be ohmic, also called gap junction, or chemical, called synaptic. Gap junction connections induce a current from cell i with voltage V_i to cell j with voltage V_j as $g(V_i - V_j)$, where g is a conductance. Synaptic connections of ionotropic type bind a chemical, called a neurotransmitter, released from the end of the presynaptic cell, to proteins penetrating the cell membrane of the postsynaptic cell. There are two classes of synaptic connections, excitatory and inhibitory. The former receives neurotransmitters and allows a flow of ions into or out of the postsynaptic cell that tends to raise the voltage across the membrane. Sufficient increase in this voltage may cause the postsynaptic cell to produce an action potential (also called a spike) allowing communication to other neurons. An inhibitory connection tends to lower the membrane potential and thus moderate the receiving, or postsynaptic, cell.

In Figure 3.1 depict a schematic of a quite common excitatory synapse found in mammals. The neurotransmitter, glutamate, binds to two different receptors, known as AMPA and NMDA. The AMPA receptor binds the glutamate in about 0.5 ms. Binding changes the conformation of the AMPA and allows sodium to flow into the postsynaptic cell, raising its membrane voltage. The glutamate unbinds in about 1.5 ms, so the voltage response in the postsynaptic cell is a small pulse with amplitudes of a few mV of about 1 or 2 ms duration. Glutamate also binds to the NMDA receptor, and this takes less than a millisecond. It takes 100 to 120 ms for the glutamate to unbind from NMDA. NMDA, however, in normal conditions is blocked by a magnesium ion that rests within the NMDA protein. This blockage is quite sensitive to the membrane voltage V and the magnesium concentration

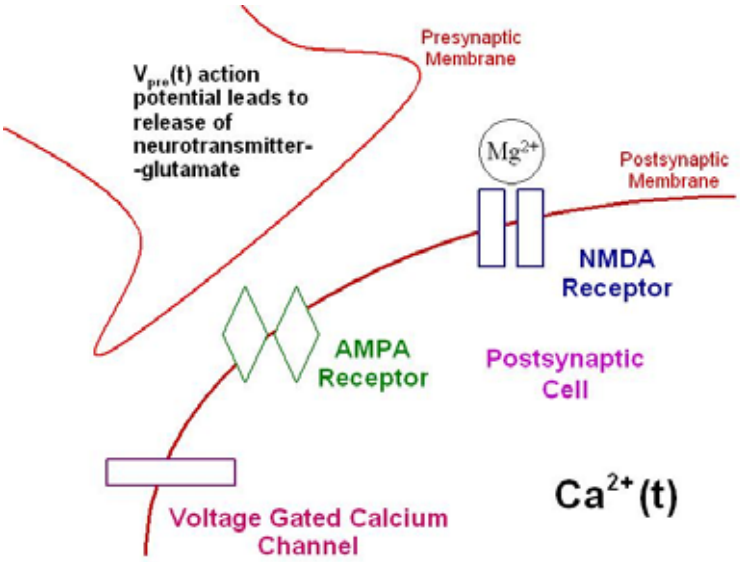

Figure 3.1: The case of the glutamate system, is illustrated. Other types of neural conncections involve other neurotransmitters, including other neurotransmitters include acetylcholine, norepinephrine, serotonin, dopamine, GABA, glycine. Schematic of excitatory synaptic connection from presynaptic cell action potential to postsynaptic cell.

$[M_g^{2+}]$. The blockage goes as

$$B(V) = \frac{1}{(1 + 0.288[Mg^{2+}]e^{-0.062V/mV)}}.$$

Thus, as the voltage rises due to sodium ions flowing into the cell through the AMPA receptor, the magnesium block is lifted, and ions can then flow for a long time through NMDA into the postsynaptic cell. The critical part of this reaction sequence is that NMDA is very permeable to calcium ions, so during the long, 100 or so ms, NMDA remains unblocked, allowing calcium flow into the postsynaptic cell.

Cells have a high affinity for free calcium. The concentration of calcium ions in a mammalian cell is $\approx$ 100 nM while outside the cell it is 1.2 mM. This means there is a large pool of Ca to flow into the cell. Once in the postsynaptic cell, Ca^2 initiates various biochemical pathways, and is itself taken up by intracellular stores in 10 to 20 ms.

Within the postsynaptic cell, there are (many) competing mechanisms induced by the Ca influx. One pathway involves kinases of various sorts, which act to stimulate the conductivity of AMPA, and the others involve phosphatases that act to reduce the conductivity of AMPA receptors. The former leads to potentiation of AMPA that can be very long lasting, known as Long Term Potentiation or LTP, and the other leads to depression of AMPA, which can be very long lasting, known as Long Term Depression or LTD.

The AMPA/blocked-NMDA combination responds quite differently to input signals of different frequencies and different temporal patterns. A low frequency stimulus, say less than about 10 Hz or 100 ms timing patterns, induces LTD, while higher frequency inputs lead to LTP. The reason is more or less clear: at low frequencies the stimulation of AMPA is infrequent enough that the NMDA block is not removed long enough to allow much Ca to enter the neuron. At high frequencies, the behavior switches, with a crossover in the neighborhood of 10 Hz.

LTD and LTP are separable

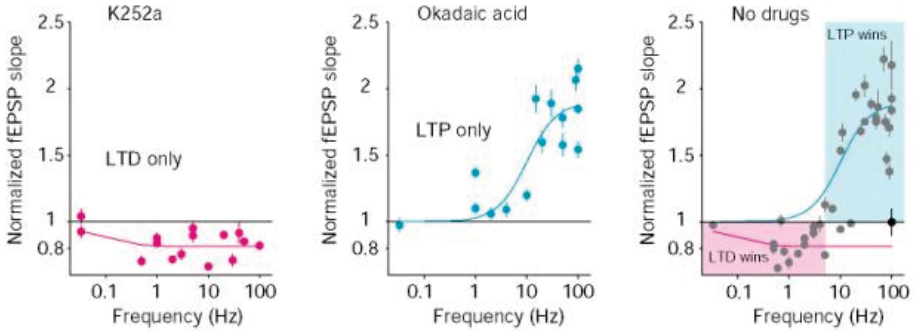

Figure 3.2: Experiments blocking kinases (LEFT) leading to LTD; blocking phosphatases (MIDDLE) leading to LTP; and no blocks (RIGHT) showing synaptic changes as a function of frequency. 1.0 is baseline: no change. Laboratory of S. Wang; Princeton

Further experiments which present a spike (or action potential) through

the presynaptic cell at time t_{pre} and induce a spike in the postsynaptic cell at time t_{post}, lead to changes in the AMPA conductivity as a function of $\delta t = t_{\text{post}} - t_{\text{pre}}$ which contains both LTD and LTP depending on how much Ca^2 is admitted during the time interval.

The full process of LTP/LTD and their effect on memory (AMPA conductivity at a dendrite receiving signals from other neurons) takes place in three stages: (a) **induction**, the initiation process bringing calcium into the postsynaptic cell. This may last as short as 10 ms and as long as 100's of ms; (b) **production**, during which processes in the postsynaptic cell induced by the elevation of intracellular calcium affect the dynamics of individual, and populations of, AMPA receptors (2). These processes last 10s of minutes, and their consequences may be present for days or longer. (3) **consolidation**, during which the information that a change in the strength of synapses at dendritic spines, perhaps distant from the main cell body, is brought to the nucleus, where genetic dynamics alters the mRNA transcribed and sent on to ribosomes for required protein production. The time scale for these processes is long compared to the first two, and may last the life of the animal.

The mechanisms for each of these stages is not known in detail, and neuroscientists and psychiatrists are is actively exploring various hypotheses on how they work. What has all this to do with learning and memory? The broadly accepted connection between changes in wiring of a network, i.e., "the brain," and changes in synaptic strengths induced at the cellular level, associates these cellular observations with implications for behavior. This is a long leap, however plausible. It also suggests that if one wishes to influence behavior, then operations at the cellular level are one place to start.

3.2 Training Effectiveness

The term brain plasticity refers to the fact that the synapses in the

brain can undergo change, i.e., that 'rewiring' or refining of brain function can take place. Until about 20 years ago this plasticity of the brain was thought to decrease markedly after youth and that it was thought that the brains connections between neurons became fixed in one's youth and very hard to change thereafter. This idea has been convincingly dispelled over the past 20 years, and idea that the brain retains its plasticity throughout life is considered settled science – you *can* teach an old dog new tricks. The plasticity of the brain allows one to consider two aspects that are very important to a military enterprise:

- Recovery from wounds and accidents involving the brain
- Neuroplasticity-based methods to enhance cognitive effectiveness.

In terms of recovery from wounds to the brain successful results abound demonstrating the exploitation of brain plasticity for therapy, for example recovery from stroke (Heiss, et al., 2005; Johansson, 2000) and treatment of aphasia – a loss of the ability to produce and/or comprehend language [29]. In terms of exploiting brain plasticity for enhanced cognitive function (training itself exploits brain plasticity); the issue here is, can special neuroplasticity-based training enhance cognitive effectiveness beyond what can be accomplished using only the material in the training exercises? In this section we will discuss some basic neuroscience aspects of neuroplasticity, note the successful exploitation of brain plasticity in therapy for brain injuries, and how neuroplasticity-based methods are being used with some success for enhanced training effectiveness and cognitive capability.

Brain plasticity basis: As discussed above (Section 3.1) and below (Section 3.3), long term potentiation (LTP) influenced by excitatory postsynaptic potential (EPSP) is the cellular basis for brain plasticity. In summary, LTP is an increase in the strength of a chemical synapse that lasts from minutes to several days. Research, beginning in the 1960's, indicates that LTP is one of the major mechanisms by which learning and memory are accomplished

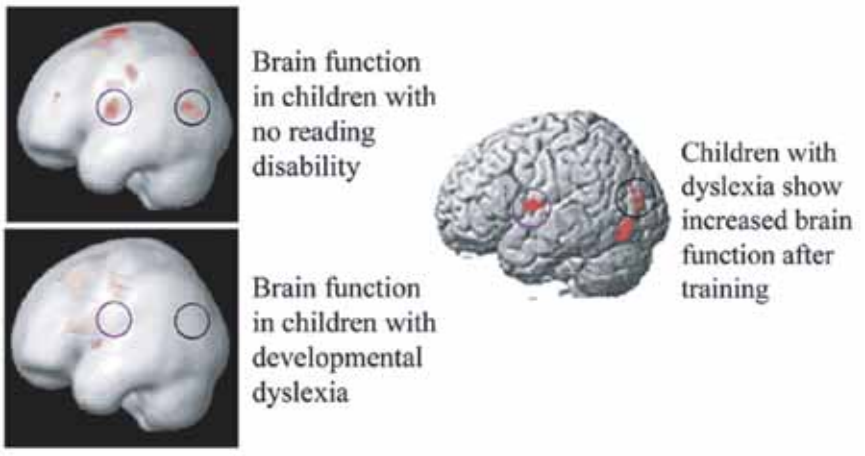

Figure 3.3: Functional magnetic resonance imaging (f-MRI) of brain activity in children with dyslexia and without dyslexia while rhyming words (left panel). Note the lack of brain function in circled areas in the dyslexic children. The results after special training for the dyslexic children is shown at right where the brain function in dyslexic children is improved to be more like normal children. [34]

in the brain. What we are most interested in here is changing the structure of LTP, i.e., exploiting brain plasticity, and doing it by special training. An important aspect of LTP, indicating its relationship to learning, is its stability over periods of months to years.[32] Drug-based enhancement of LTP is discussed in Section 3.3 below.

Brain plasticity and special training for recovery from brain injuries: The bottom line here is that due to the plastic nature of the brain, neural connections can be permanently rewired and refined by the right repeated stimuli to aid in recovery from disabilities and brain injuries. An interesting example from Temple et al. [34] in the use of special training for treatment of dyslexia shows how the function of the brain is revealed by f-MRI (functional Magnetic Resonance Imaging) images of the brain. In Figure 3.3 below we see how training-based remediation alters the brain function of dyslexic children, bringing them closer to normal children. This is among the many pieces of evidence that special training can alter brain function to aid in the recovery from both accidents and learning handicaps.

A very interesting example of using special training to exploit brain plasticity to aid in recovery from stroke involves robotic training [30]. In this case a 20-year-old woman, Mary O'Regan, had a stroke related to a head injury suffered in a dirt bike accident. She eventually recovered the use of speech and was able to walk again and returned to a life in which her left side remained mainly numb and her left arm was useless. This year, some 20 years later, she is learning to use her left arm again with the aid of a new robotic device called the Myomo e100, developed by John McBean and Kailas Narendran at MIT. This device, shown in Figure 3.4 below, senses weak electrical activity in the muscles of the patient's arm and uses these signals to provide, "just enough assistance that they can complete simple exercise, like lifting boxes or flipping on light switches. By practicing such tasks, patients may begin to relearn how to extend and flex the arm, rebuilding and strengthening neurological pathways in the process." Mary reported that the use of the device was, "... extremely encouraging." and that she was able to practice simple tasks like folding towels, opening drawers and lifting objects from one position to another. A small study using the e100 device at the Spaulding Rehabilitation Hospital in Massachusetts showed an average 23% improvement in upper extremity function after 18 hours of training in a 6-week period.[33] The success so far has led to approval by the Food and Drug Administration and planning of studies to extend applications to spinal cord injures and brain trauma, including patients who are military personnel. wounded in Iraq. Further examples abound in the literature regarding brain plasticity and recovery from stroke and other mental afflictions. e.g., reviews by Heiss and Teasel [25] and Johansson [26].

Brain plasticity and special training for increased cognitive function in normal, healthy adults: it is known that there is an age-related decline in cognitive function of the brain (ARCD), along with losses in brain processing speed and declines in the effectiveness of perception and memory. This decline is thought to be due to poorer signal-to-noise conditions and a down-regulated neuromodulatory system function in older brains. Since neuro-

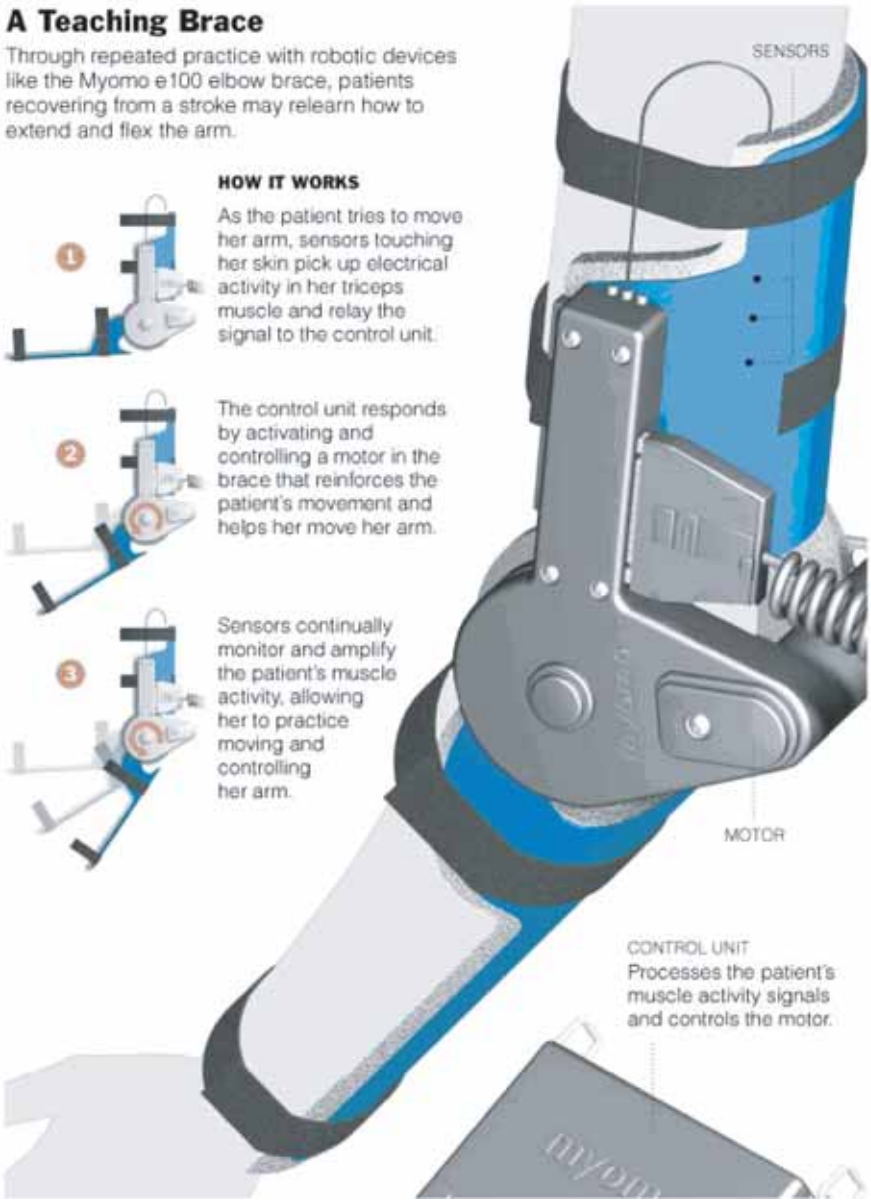

Figure 3.4: The Myomo e100 robotic device senses weak electrical activity in a patients arm muscles and uses this signal to actuate a mechanical unit to move the lower arm as shown in the diagram at left. This assist allows patients to retrain their own muscle control system to regain a measure of use of the arm to do tasks they had been unable to do after the stroke. After New York Times (July 10, 2007).

modulator regulation is thought to be a result of neuromodulator-synapse interaction, could exercises that "rewire" the brain through training exercises reverse ARCD by making use of brain plasticity? More generally nearly everyone would be pleased to increase their personal cognitive abilities, regardless of their current cognitive effectiveness. An hypothesis has been developed that special training can reverse age-related decline and help mature adults in general. Some quantitative evidence in support of this hypothesis has emerged. An example is the work of Mahncke [28].

In the Mahncke et al. study a group of 182 healthy adults from 60 to 70 years old were divided into three experimental groups:

ET – the group given the experimental 'brain training'

AC – the active control group that were carefully matched to the ET group, but received no brain training

NCC – the unmatched, no-contact, control group.

For the ET group the objective of the experiment was to intensively exercise aural language reception accuracy with the idea of altering the down-regulated neuromodulatory structures in the brain using a series of training sessions. The ET subjects were trained with sensory and cognitively demanding exercises where, to make progress in tasks, the participant must perform increasingly more difficult stimulus recognition, discrimination, sequencing, and memory tasks under conditions of close attentional control, high reward, and novelty. No further description of the training exercises was published. The 62 ET subjects were trained in 40, 1-hour sessions and then tested on trained and non-trained skills with a follow-up testing three months later.

In the area of skills that were directly trained by the exercises the following table shows the results.

Improvement	Exercise				
	Speed of processing	Spatial syllable match memory	Forward word recognition span	Working memory	Narrative memory
Participants showing improvement	93%	77%	91%	80%	91%
Average improvement	41%	10%	18%	13%	18%

It is readily apparent that, on the trained skills, most subjects benefited and that the improvement in processing speed was excellent, with substantial improvement in other areas.

Non-trained skills were assessed by using a standardized neuropsychological measure of memory function, namely a global auditory memory score. The results for the experimental (ET) and control groups are shown in the table below. We find that for this broader measure of memory performane

Group	Pretraining	Posttraining	Difference *P* value
ET	48.9 ± 1.3	51.2 ± 1.2	2.3 ± 0.9 *P* = 0.019
AC	50.2 ± 1.2	51.2 ± 1.2	1.0 ± 0.9 *P* = 0.29
NCC	51.2 ± 1.0	52.3 ± 1.1	1.1 ± 0.9 *P* = 0.22

that was not directly part of the training,the improvement in memory performance was significant, but modest. The right-hand column shows that the improvement in the ET group was statistically significant while the changes in the control groups (AC and NCC) were not significant. The P values (based on the Student t-distribution) indicate the probability that the observed difference would occur by chance given the number of subjects (degrees of freedom) used in the experiment. So the improvement in the auditory memory score achieved by the ET group (2.3 or about 5%) is statistically significant because it would be expected to occur by chance only 1.9% of the time using groups of 62 subjects. The P values of changes in the control groups would happen by chance much more often and are thus not statistically significant. A test of the cognitive improvement on the digit-span forward assessment

test continued to show the same improvement after 3 months as it did immediately after the training sessions. So the method shows some persistence.

In summary we find that training based on brain plasticity shows significant improvement in skills related to the training. The generalization that brain training improves general (non-trained) cognitive skills is statistically significant, but modest in gain. Further study is needed, especially with military-age subjects.

The brain training methodology to improve cognitive function has also reached the public sector in terms of applications to both school children (e.g., Fast ForWard) and the general population (e.g., Nintendo's "Brain Age"). However, few of these commercial products are rigorously designed or evaluated. Scientific Learning (http://www.scilearn.com/) markets Fast ForWard as a tool to improve reading and cognitive skills and has been successful in placing Fast ForWard in many schools across the country with what they document as very useful improvements in reading skills, e.g. see results in the Dallas Independent School District [31]. However, the documentation on specific Fast ForWard applications is not from independent, outside investigators, so far as we have been able to discover. Experiments having control populations, an independent environment, and conducted by independent investigators, are needed to confirm the vendors results and to investigate long-term improvements.

Assessment of special training methods: One suggestion for future testing of brain training methods that exploit brain plasticity or other avenues is to select a set of "general intelligence" tests to validate methods for increasing brain cognitive function. There is a need for assessment metrics as well as establishing baselines for comparison. Fortunately there are a number of suitable IQ or aptitude tests already in existence. Some have already been widely used on military populations. Three candidate tests for consideration (already used for military populations) are:

- ASVAB = Armed Services Vocational Aptitude Battery
- WAIS-III = Wechsler Adult Intelligence Scale-III
- MAB = Multidimensional Aptitude Battery.

An example of the application of these tests is given in work by Kratz [27].

Summary of Special "Brain Training" to Improve Cognitive Brain Functio: We summarize the findings and recommendations as follows:

State of the Art:

- Effective retraining of damaged or disabled brain function is established and in clinical use.
- Brain training exercises for enhancement of brain function in mature healthy adults shows statistically significant, but modest, results so far. Proliferation of brain training techniques into the public sector is now in progress.

Prognosis:

- Techniques for retraining after injury or handicap are currently in medical practice and will continue to evolve and broaden in their use.
- Techniques for normal, healthy adults have been studied in a few cases with somewhat encouraging results, and are moving into commercial application. The commercialization should provide new information and some 'fuzzy' sorting out of methods is likely to occur – innovation coming by trial and error. However, more scientific research on healthy adults, especially in youth to middle age is needed to fill gaps in knowledge, e.g., can it help in learning multiple languages?

Military Impact:

- Special brain training will continue to be useful in treating wounded and veteran military personnel, e.g., brain trauma recovery. This methodology should be put to full use in treating the large number of wounded emerging from the Iraq war as well as previous wars. Successful results are emerging for people with injuries from decades before, e.g., concussion and stroke victims.

- Results of scientific studies so far indicate significant, but limited, impact of brain training for enhancement of brain function in mature adults. However, possible use in enhancement for personnel with specific needs, such as deficient language skills and possibly multiple language learning should be considered. Results from existing applications to school students claim improved language and cognitive skills [31]. However, further study, independent of the vendors of the tools, are needed to verify these claims of success.

3.3 Pharmaceutical Enhancement

The development of neuro-pharmaceuticals to treat psychiatric disorders, and disabilities such as attention deficient hyperactivity disorder (ADHD), is a dynamic area of research, with major advances in medical treatments resulting over the last decade. As new drugs are developed, the detailed studies involved always reveal effects peripheral to the main therapeutic uses, many of which may have significant potential applications. One well-established class of neuro-pharmaceuticals acts to increase the concentration of the neurotransmitter in the intercellular medium, and thus acts as an overall stimulant for neural function. Some examples of these drugs are listed in Table 2, including their approved uses. All affect either or both cognition and alertness, and all have substantial off-label uses for ameliorating sleep deprivation,

and/or as study aids. Amphetamines are approved, under close control, for maintaining alertness in some military operations.

Table 2: Prescription drugs that act as neural stimulants.

Amphetamine	Increase norepinephrine, dopamine and serotonim release	ADHD, narcolepsy, chronic fatigure syndrome
Methylphenidate (ritalin)	dopamine re-uptake inhibitor	ADHD, narcolepsy, chronic fatigue syndrome
Modafinil (Provigil)	Dopamine & norepinephrine re-uptake inhibitor + possible action on neuropteptide hormones	Narcolepsy
Donepezil (Aricept)	Acetylcholinesterase inhibitor	Memory loss in Alzheimer's disease
Galantamine (Razadyne)	Galantamine (Razadyne)	Memory loss in Alzheimer's disease

The applications of donepezil and glantamine for treating memory loss in Alzheimer's disease has led to interest in their use to enhance cognitive performance [35]. However, a new class of drugs may superced these older medications. The new drugs specifically impact long-term potentiation or, in other words, facilitate the physiological changes of brain plasticity. Some of these new drugs have has undergone substantial testing, and are now under consideration for FDA approval. One class of these drugs, ampakines, is described below, to illustrate the differences with respect to stimulants, and the potential new effects.

3.3.1 Ampakines

The neurostimulators listed in Table 1 increase the concentration of neurotransmitters, thus increasing the ease of creating an action potential. A more controlled response is possible if instead the action of the neuroreceptors is modulated to create a stronger response to a normal physiological level of neurotransmitter. One approach to modulation of the glutamate neuroreceptors uses a class of simple chemical compounds called ampakines. These

molecules alter the conductivity of AMPA receptors by, in effect, modifying their structural conformation when glutamate is docked on the AMPA, as illustrated in Figure 3.5. The chemical (patch) and electrical (synapses) responses as a function of time are shown in the lower panel of the figure, with the normal response as the upper curves and the ampakine-modified response in the lower curves.

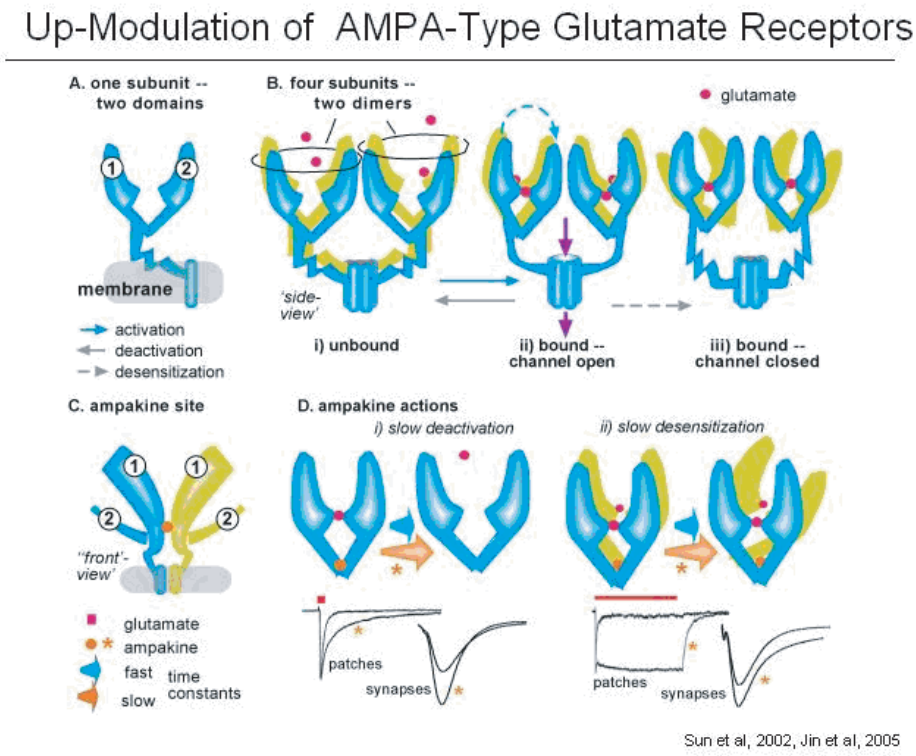

Figure 3.5: Mechanisms for actions of ampakines. Upper row: glutamine present in the synaptic channel binds to the AMPA neuroreceptors, causing a structural change that opens a channel through the cell membrane. If the synaptic concentration of glutamate decreases, unbinding occurs and the channel closes (deactivation). If the concentration of glutamate remains high for a long time, a second conformational change occurs, closing the channel (desensitization). Lower row: Ampakine binds cooperatively with glutamate and increases the time constants for both deactivation and desensitization. The graphs show the chemical and electrical responses to short and long glutamate exposures (indicated by red bars) for normal AMPA action (upper curves), and ampakine-modified AMPA action (lower curves).

There are many consequences of enhancing the activity, magnitude of voltage response, and time course of response at AMPA receptors, as shown in Figure 3.6. Every biochemical action is linked by feedback and regulatory

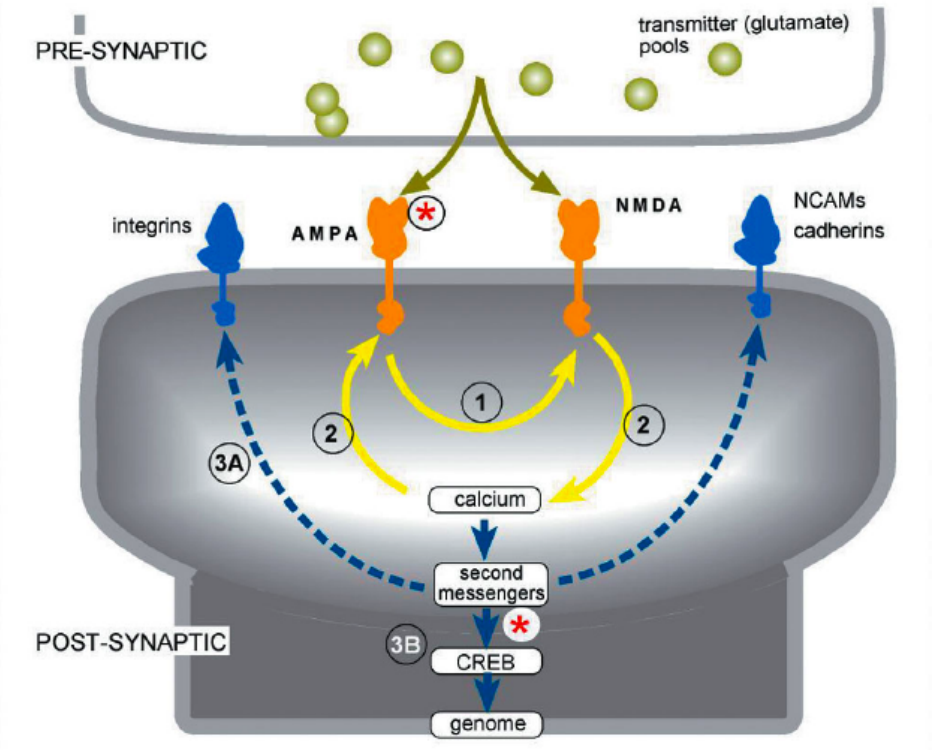

Figure 3.6: Interconnected biochemical cycles. Ampakine-induced increase in AMPA activity directly affects NMDA response in admitting calcium ions. Increased Ca^{2+} concentration increase subsequent AMPA response (path 2), and cause long-term changes in the effectiveness and number of AMPA receptors (paths 3A and 3B). Path 3A involves changes in the cytoplasmic region near AMPA. Path 3b involves gene-signaling pathways including the CREB transcription factors. Figure from reference [36].

networks (only a few of the network paths for the glutamate system are shown in Figure 3.6. [36, 37, 39] For ampakine-mediated AMPA response, there are cooperative effects from the increased Ca^{2+} flow through the NDMA receptors, and the subsequent production of messengers that signal changes in gene expression. Responses in the form of increased protein production (e.g. additional AMPA) can occur on the time scale of minutes, and new synapse formation can occur on the time scale of tens of hours.

3.3.2 Effects of ampakines on cognition

Both the biochemical effects of ampakines and their effects on performance of cognitive tasks have been tested extensively [36, 38, 40]. Direct confirmation of improvements in LTP and modification of biochemical pathways have been demonstrated. Both rats and primates have been subject to behavioral tests to evaluate the correlated effects of ampakines on performance, with tests including subjects of various ages, and subjects with disease-induced impairment of cognition. Of particular interest for possible uses in non-disease related human peformance modification have been studies on healthy young adults. One example, involving cognitive tests for Rhesus moneys, is illustrated in Figure 3.7. The upper panel illustrates the test, in which first an image is shown, such as the one to the left, then after a certain delay a group of images (2 to 6 images) is shown, such as the group to the right, from which the subject selects the matching image. The center panel shows a comparison of the response for monkeys without (left) and with (right) ampakine treatment. There is a clear improvement in performance, correlated with changes in fMRI patterns, when the monkeys were treated with ampakines. The performance gain was

The potential of using ampakines to ameliorate the effects of sleep deprivation was also tested, as shown in the lower panel of Figure 3.7. Comparison of the Normal Alert and Sleep Deprived results to the right shows decrements in performance after 30-36 hours without sleep. The decrements are most severe in the tasks that the monkeys were originally best at (e.g., short time delays). Repeating the tasks with sleep-deprived monkeys that had been administered ampakines, as shown in the lower right, restored performance to levels comparable to or better than those for well-rested monkeys without ampakine treatment. This preliminary result is unsurprising, given that stimulants such as amphetamines and modafinil, that enhance neurotransmission, are known to be effective for combating the effects of sleep deficit. If the amapkines prove useable for extended periods without adverse side

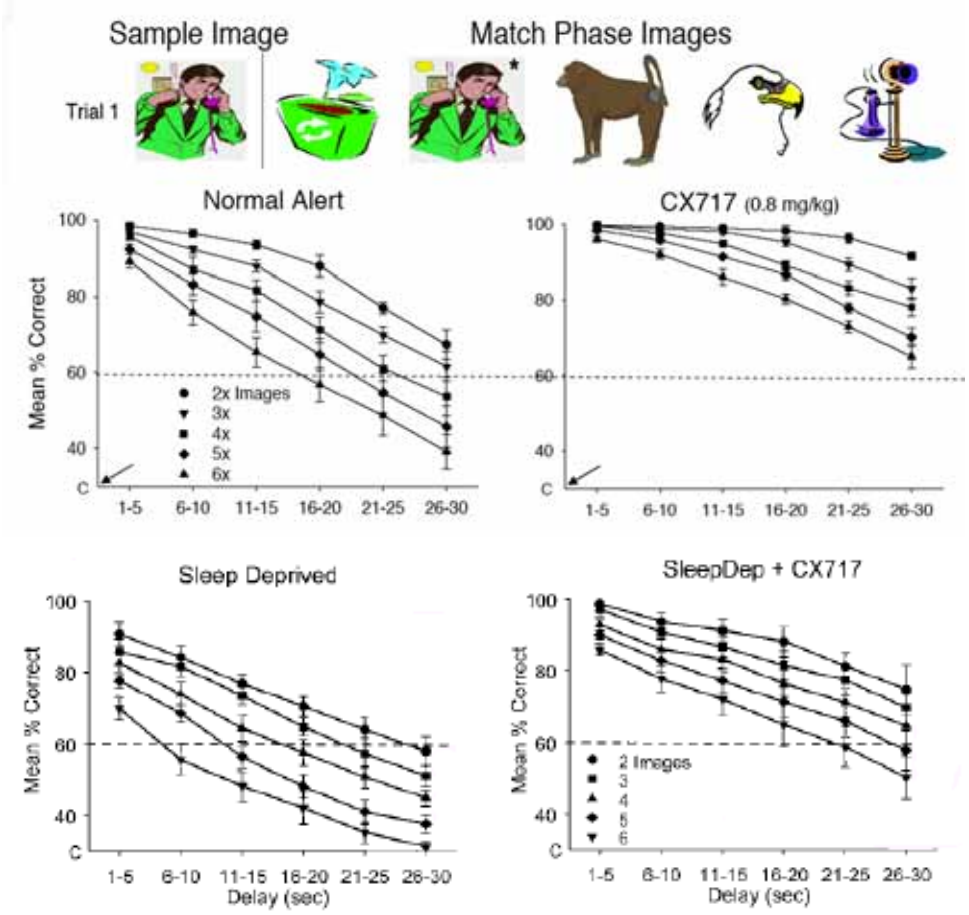

Figure 3.7: A delayed match-to-sample test is illustrated in the top row. The first image is shown, and then after a time delay, a group (2 through 6 images) of images is shown. The subjects score is simply the number of times that the correct image is chosen. Center row: average performance results for 9 monkeys each performing 150-300 selections per session. Left and right graphs show results with and without administration of ampakine. Bottom row: results for monkeys subjected to 30-36 hours of sleep deprivation before tests.

effects, it is likely that they will also find application in chronic fatigue syndrome.

3.3.3 Continuing development of neuromodulators

Many medical treatments are under development that use the strategy of modulating the neuroreceptor response or regulatory network [36, 38], as shown in Table 3. While the drug development and approval process is being carried out for medical conditions such as ADHD and Alzheimer's disease, the correlated potential of these drugs for improving normal cognition is well recognized. As with the stimulants listed in Table 2, there is certain to be extensive off-label use and experimentation with these drugs when they are approved for prescription use.

Table 3: Modulator Drugs Under Development.

Name	Biochemical Action	Approval Status
Ampakines	Modulate AMPA glutamate receptors, enhance LTP	Phase IIB studies
Phosphodiesterase inhibitors	Improve CREB activation of protein synthesis, enhance LTP	Phase IIA studies
Bryostatin	Protein kinase C activator, enhances protein synthesis and LTP	Approved as cancer treatment, under clinical trials for memory function

It is not at all clear that vast improvements in normal cognition will be achieved with these drugs, and unexpected consequences may well occur when off-label (or illegal) uses of these drugs are explored. The proposals for intervening at the cellular induction stage of enhancement or decrement of synaptic conduction strengths involves at least two broad assumptions. First, the detailed connection between actions at the cellular level on one or a few neurons and the manifestation of these actions through a complex network of neurons to functional behavior is conjectural. Neither the anatomical

nor the electrophysiological details of the network are known, much less understood. How the network responds to differing inputs, possibly learning signals, possibly threats from predators, possibly signals indicating pleasure, is not understood either.

Secondly, the application of neuromodulators, such as ampakine and the others mentioned, are broad through the brain and thus are not targeted to specific brain regions—not yet anyway. Since the reports quoted by Lynch in themselves show that different regions of cortex respond differently to the same neuromodulators, the overall implications of any type of neuromodulator is far from being known.

To adopt an optimistic view, however, it is quite possible that these issues will be resolved with finer and finer detail by experimentation correlating detailed investigations of the biochemical interconnections, brain-area response and cognitive response. As with most things one wishes to know about complex networks, even many much simpler than our brain, the techniques for comprehending these networks are not well developed, and the path ahead is itself complex, and probably long. On a shorter timescale, however, it is virtually certain that empirical experimentation will occur using drugs approved for medical applications. Such experimentation will reveal risks, such as unexpected side affects, and also will reveal the range of human performance modification (good or ill) that can be achieved with the present imperfect understanding. The potential for adversarial threats arriving from such developments will be discussed in the following section.

3.4 Summary

Advances in neuroscience are just beginning to yield a mechanistic understanding of learning. As quickly as advances in this field are released, there are proposals and advocates of how to interpret and use the results to

improve education and training [12]. Many of these proposals are based on limited or poor understanding of the significance of research results. However, there are increasing efforts to develop new training tools that actually draw on scientifically tested procedures to improve the basic elements of cognition. Some of these efforts are driven by medical needs in helping rehabilitate patients after strokes or brain trauma. Other efforts are specifically focused on helping those with learning disabilities, and still others on those experiencing age-related decreases in cognitive function. There is little research or evidence concerning the effects of focused training on healthy, young adults functioning at normal cognitive levels.

However, effective training is a priority in military preparedness [3, 4]. The US military will certainly test whether, and to what extent, the new lessons of neuroscience can be used in military training, and it is reasonable to expect that adversaries will do so as well. We do not expect the development of super-soldiers as a result of improved training, although enhanced military capability can certainly be expected. However, unexpected adversarial behavior could result if training included behavior modification (e.g., for increased aggressiveness or decreased empathy). Thus one strong recommendation of this study is that the US should develop a technical knowledge base concerning scientifically based training tools, especially as applied in behavior modification. This knowledge base should be combined with information-gathering and analysis concerning the training techniques (both civilian and military) in adveraries' cultures.

Existing neuro-pharmaceuticals such as modafinil are used rather commonly (often via illegal use of prescriptions) as study aids, and indeed have scientifically-based mechanisms to explain why they can enhance the effectiveness of learning. However, any college professor can attest that such amateur "human peformance modification" has not yet caused any remarkable upward displacements in the distributions of student performance. The US military specifically does not use such drug-enhanced training, although there may also be individuals who pursue this approach on their own initia-

tive. Whether any adversaries use such cognition aids in training is unknown. However, their use in combination with carefully designed training could be employed as discussed above by adversaries to modify their troops' behavior.

Developments in new types of neuro-pharmaceuticals, based on modulation rather than stimulation of neurotransmission, show promise for enhanced treatment of medical conditions related to cognition (e.g., ADHD, Alzheimer's disease). It seems likely that these drugs, once fully developed for prescription use, will also develop applications in treating other cognitive disorders and sleep disorders. Again, adversaries may experiment with the use of such drugs in combination with well designed training programs. While the potential effectiveness of such programs is not yet known, the technical developments in neuropharmacology will continue to push the limits of what may be achievable. Thus another strong recommendation of this report is that the US military should maintain a strong, technical awareness of the medical and popular uses of neuro-pharmaceuticals in the US, and develop intelligence about popular and military applications in potential adversaries' cultures.

4 BRAIN COMPUTER INTERFACE

The use of surgically-added mechanical components to the human body, for instance replacement of joints or use of pace-makers, is widely accepted for the remediation of medical problems. As with pharmaceutical interventions, it is natural to consider whether such procedures could be carried beyond medical intervention. In particular, the possibilities of enhancing normal human performance, or adding new capabilities in strength, endurance, sensing or cognition, are common popular themes. As in the case of pharmaceutical intervention, the most useful basis for evaluating the potential for unexpected consequences is the state-of-the-art in medical developments.

Here we will address two broad classes of physical interventions, non-invasive and invasive interfaces to the neural system. Non-invasive interfaces involve external electromagnetic stimulation of neural response or external sensing of the electromagnetic signatures of neural activity. In non-invasive interfaces, the interactions with the neural network are non-specific and thus limited in controlled effect. Invasive interfaces involve direct surgical connections to the nervous system, to allow sensing of neural signals, input of sensory stimuli, or to regulate neural activity. In the case of invasive interfaces, the parallelism of output or inputs is limited by the limited knowledge of the nature of the neural network and by the complexity of making multiple connections surgically. In both cases, significant improvements are possible for medically impaired subjects. However, the ultimate performance now achievable with such interventions falls far below average normal human performance.

In the following we will present one example each of invasive and non-invasive interfaces, to illustrate the physical basis for the present limitations of their performance and the potential for future improvement. The potential for non-medical uses of such interfaces will be discussed in the context of popular interest (e.g., similar to non-medical uses of pharmaceuticals).

The potential for unexpected threats arising from adversarial military use of invasive interfaces is likely to be limited to adversaries with high technical capabilities, and on a long time scale. Some examples will be presented.

4.1 Non-Invasive Brain-Computer Interface

Medical research using non-invasive electromagnetic interfaces is now dominated by two "write-only" techniques, transcranial magnetic stimulation (TMS) and direct current stimulation (DCS), and by many "read-only" techniques, already mentioned in the introduction, including electroencephelography (EEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). TMS is implemented using a current loop positioned outside the skull. Pulsed current in the coil creates transient magnetic fields and corresponding eddy currents in the neural networks in the brain. The technique has limited spatial resolution, and thus areas of specific neural function (even if they were well known) cannot be selected for specific excitation. The technique has been investigated extensively for treatment of severe psychological disorders, such as drug-resistant depression. However, because of the large variability in patient response (see Section 2.3 on statistical issues), and the inability to relate results to fundamental physical mechanisms, definitive effective treatments have not been obtained [44]. The alternative approach of DCS has attracted attention in part because it is simpler to apply and offers fewer safety concerns. The technique simply involves positioning a pair of electrodes transcranially, and applying a low current on the order of tens of milliamps. The current flow increases synaptic excitability, and can result in muscle stimulation and changes in mood. Transcranial DCS is under investigation as therapeutic treatments [45], although it appears to have weak statistical correlations similar to TMS. However, due to its ease of implementation, it is quite likely that commercial or recreational experimentation with DCS may occur.

Of the non-invasive "brain-reading" techniques [46, 47], only EEG is readily implemented outside of a sophisticated research setting. In EEG, electrodes on the skull pick up electrical signals due to neural activity. The signals can correspond to muscular activity, such as eye motion (visually evoked potentials – VEP), or can arise from independent brain activity [48]. Independent brain signals are characterized by frequency bands in the range of 1-100 Hz. Because rudimentary sensing requires relatively inexpensive equipment, commercial products have been developed that employ EEG feedback as a relaxation tool. More sophisticated instrumentation is also widely used in medical diagnostics and research. In contrast, the use of EEG signatures for arbitrary control activities is a less natural, and thus much more difficult, application.

The concept of "brain-controlled" exterior action through the use of the externally transmitted electromagnetic signals of the central nervous system is a compelling theme of popular fiction, as well as powerful medical hope for those with muscular disabilities. The potential and limitations of EEG for external control is well illustrated by state-of-the art research into developing interfaces for paraplegics to communicate via computer screen controls. Development of a serious ability to create controlled responses requires multiple sensors of the EEG signals, which is accomplished through the use of electrode arrays, as illustrated in Figure 4.1.

The goals to be accomplished using the outputs of the electrode array are to select or move objects on a computer screen. Generally, the subject must minimize muscular activity, including eye movement, to prevent obscuring the weaker signatures of independent brain activity. One approach to this problem has been to train the user to modify his or her EEG signal to specific patterns matched to specific responses. This requires prolonged and extensive training, with variable success among different individuals. Another approach is to have the users define signals corresponding to specific desired responses, and use software to analyze the signals and create the desired response. The latter approach can be accomplished with relatively

Figure 4.1: A network of 128 electrodes used to map the spatial distribution of EEG signatures around the skull. From reference [49].

little user training. The initial steps in signal processing used in evaluating the raw EEG sensor input are illustrated in Figure 4.2. The input signature was monitored over a time interval of about 1 second. The signals were then processed to remove artifacts and noise patterns prior to Fourier analysis. The relatively long measurement period needed to obtain the low-frequency signatures imposes a significant limitation on how rapidly EEG-control can transfer information.

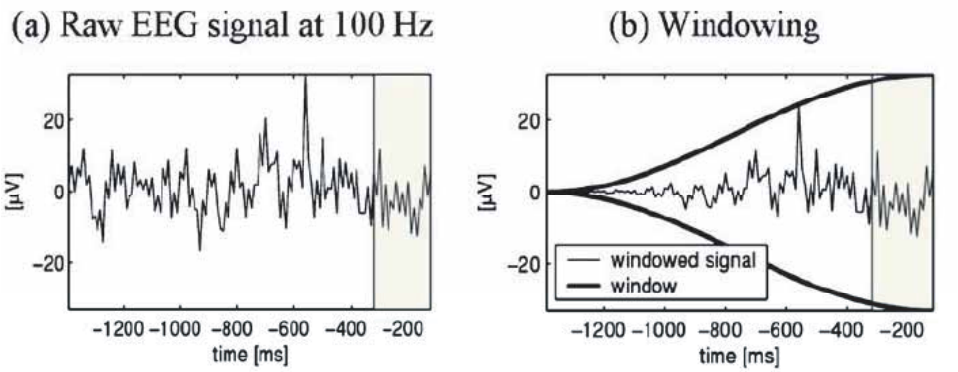

Figure 4.2: Illustration of temporal variation of a raw EEG signal with a dominant 100 Hz component, and windowing used to remove noise and artifacts. From reference [49].

The first step in "recognition" of a specific control signal is to extract the Fourier components and identify which frequency bands are related to each control action for each subject. The individual variability observed for the EEG signature for the same task is shown in the two columns in Figure 4.3, beginning with the Fourier spectrum of the EEG signals averaged over all the sensors. The results of applying a filtering function to the raw data are shown in the second row. The "background" spatial distribution of the signals from all the sensors distributed over the skull is shown in the third row. The signal is the average over all the control actions that need to be discriminated. Rows 4 and 5 show the background-subtracted spatially-distributed signals for two different control actions. Again, the significant variability among subjects is evident. To optimize selection of different control signals, a final filter design is implemented. The filter is designed to identify the maximal differences between different control signatures. The design is based on the identification of the correlations between different signatures, one of which is shown in row 6 of Figure 4.3.

This approach requires a large computational investment, now feasible due to routine implementation of microprocessor arrays. The result is promising by the standards of providing communications channels for severely disabled individuals. The rate of information transfer is tens of bits per minute, with accuracies varying among individuals from 65 to 98% (average accuracy 88%).

Given the extreme care needed to extract a specific control signature, even under conditions where muscular activity is minimized to avoid interfering signals, the possibility for using such brain control in a military scenario is not readily apparent. A recent DARPA proposal [49] for an advanced imaging system includes a requirement for a brain interface capable of responding to subconscious recognition of a target or threat. Given the intense physical and mental activity likely to be present under operational conditions, such a signal would have to be both strong and unique in signature to be extracted for the other signatures of neural activity. The programs that are instituted

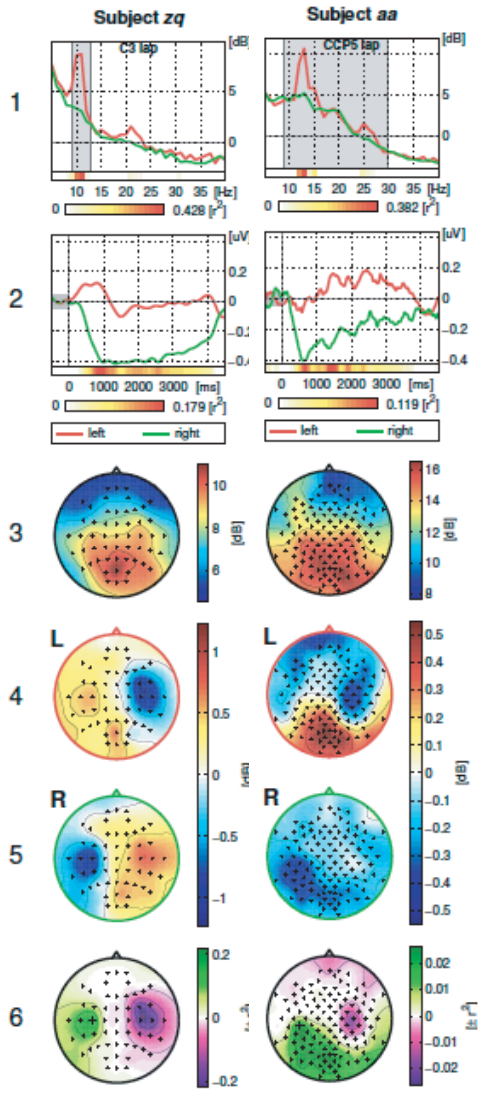

Figure 4.3: Process of developing EEG pattern recognition for individual signatures created for a specific control action. Two columns show signatures for two different individuals creating an EEG signal for the same control action. From reference [49]. Row 1: Frequency spectrum of response signal - average from all sensors, Row 2: Temporal signature after windowing and frequency selection, Row 3: Spatial distribution from individual sensors averaged over all control actions, Rows 4 and 5: Difference spatial signatures for two different control actions, with background signature defined by Row 3 subtracted, Row 6: Correlation function of the two control responses of rows 4 and 5.

under the DARPA call for proposals will provide an interesting test case for the suitability of non-invasive brain interfaces for military applications.

4.2 Invasive Brain-computer Interfaces

The limitations of a non-invasive interface seem obvious, for instance in EEG, the electromagnetic signals being used reflect in a noisy and degraded fashion the combined activity of many millions of neurons and synapses". Thus developing interfaces that more directly probe the electrical signatures of specific locations in the central nervous system, or even individual neurons or synapses, would seem an obvious path toward improved performance. Enhanced signals can be obtained with electrocorticographic electrodes that are placed directly on the surface of the brain, or through microelectrodes that can be surgically inserted into the cortex or into other components of the central nervous system [46, 47, 51], as illustrated in Figure 4.4. Surprisingly, the enhanced signal strength and specificity obtained in this way has not translated into improvements in brain-controlled actions compared with, for instance, the type of EEG interface described above.[46] It appears likely

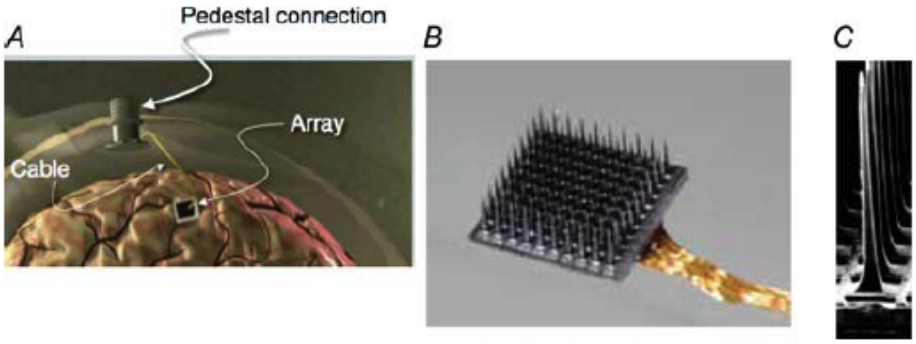

Figure 4.4: Left: A micro-electrode array shown implanted into the cortex with connections to a "feedthrough" pedestal on the skull. Center: Image of the array and wire bundle, the electrodes are spaced with 400 μm separation. Right: Scanning electron microscope image showing the shape of the electrodes. From reference [52].

that this is due to a mismatch between the expected controls to be exerted by the brain signal generated in the cortex, and the desired output action, which generally is (or mimics) muscular control. Substantial improvement in how signal origins are identified, and how signals are processed for the desired out comes is needed for predictable, high quality brain-control to become a reality.

The alternative application of the invasive brain-computer interface is to provide input to the central nervous system. Medical interventions such as cochlear implants and even retinal implants, and vagus nerve simulation to treat epilepsy and depression, all provide direct input to the central nervous system. Cochlear and retinal implants use the specific sensory nerve inputs designed for the functional remediation desired and thus have the benefit of using the neural circuitry exactly as it was designed. Vagus nerve stimulation also uses a remote nerve input, but the mechanism for controlling epilepsy or depression is not well understood, and its efficacy is variable. These three examples illustrate how far invasive brain interfaces are from the possibility of sophisticated external control of brain function. However, these three medical examples also illustrate the great progress and potential of such medical interventions, which will continue to stimulate medical understanding and technical advances in this area.

Although the present technical capabilities are not impressive, one can consider the potential that an adversary might use invasive interfaces in military applications. An extreme example would be remote guidance or control of a human being. There has been non-medical research into remote monitoring or control of animals (rats, sharks, pigeons, etc.) [53, 54, 55] with applications in research or law enforcement, with related strong interest in the popular press. The state of the art is illustrated by the results shown in Figure 4.5. Here the subject rats had electrodes implanted in the medial forebrain bundle (MFB) and in the areas of their somatosensory cortices associated with the left and right whisker bundles. Stimulation of the MFB causes a pleasure response, whereas stimulation of the whisker sensory areas evokes a

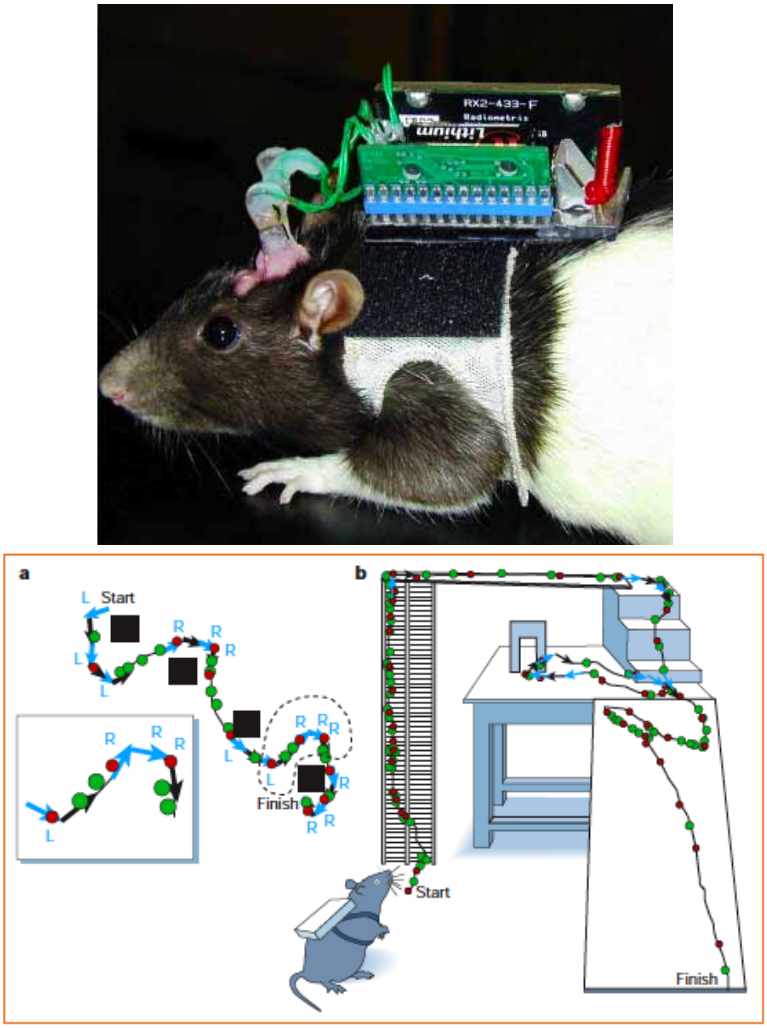

Figure 4.5: Upper panel, rat with implanted electrodes connected to external microprocessor/radio signal receiver carried in a "backpack". Lower panel, illustration of mouse motion through mazes under external stimulation by an observer with the mouse under visual surveillance. The red dots indicate rat head positions at 1-s intervals; green dots show positions of reward stimulations to the medial forebrain bundle (MFB); blue arrows show positions at which right (R) and left (L) directional cues were issued. From references [54, 55].

sensation as if the whiskers were touched. Researchers found it was possible to direct the rats to turn left or right with whisker stimuli, and the rats were trained to move forward in response to the MFB "pleasure" stimulus. With these controls the rats were successfully guided through chosen paths such as two and three-dimensional mazes.

The illustrated level of control is fairly rudimentary. However, even at this level of input, applications such as feedback during training, or providing soldiers with alerting signals, could be implemented. The training application could, as previously discussed, be used for dangerously increasing aggression or decreasing social inhibitions, and the use of direct brain stimulation could plausibly increase any affects. The alerting application would require an external observer or sensor system set up to monitor, evaluate and then transmit the alerting signal to the soldier. This would require substantial investment in technology and organization external to the nature of the link to the soldier. The potential added danger that a direct brain interface could pose (as opposed for instance to information transfer via an earphone), seems limited, given the limited state of medical understanding of how such stimuli can be used to modify brain response (such as epilepsy or depression). By following the continuing developments in the applications of brain computer interfaces in neurophysiology and psychiatry, it should be possible to maintain a realistic assessment of how such interfaces might be used in military scenarios. Given the sophistication of the equipment and medical technology needed for invasive interfaces, it seems unlikely that experiments in military applications of brain-computer interfaces will be possible outside of military establishments that have suitably well-established infrastructure.

4.3 Summary

The brain-computer interface excites the imagination in its potential (good or evil) applications to modify human performance. However, the

present reality of medical interfaces falls far short of these imaginary scenarios. While interventions such as EEG-brain control for tetraplegics or cochlear implants for hearing impairment have large positive impacts on quality-of-life for those with medical disabilities, the ultimate level of performance achieved remains far below that of a normal function. This is in part due to the early stage of development of the associated technologies, and in part due to limited understanding of the central nervous system. At this time, it is unknown how far, or in what directions, applications of brain-computer interfaces will develop.

It is possible, however, to consider various speculative scenarios in the context of present medical capabilities in brain-computer interfaces, as follows:

- **Scenario 1**:

  Speculation: Direct signals from the brain could be used to direct or alert external equipment, as an auxiliary to direct human actions.

  State of the art: External signals from the cerebral cortex, picked up either by EEG or by implanted electrodes, have severely limited information transfer rates and are susceptible to interference if the subject is not closely focused on the one task being directed. It is possible that this may reflect a fundamental limitation, as the natural function of the cerebral cortex is not directly linked to action control, but instead directs action through a complex circuit of lower-lying neural circuitry.

  Future developments: More detailed mapping of brain function, and improvements in making direct connections with implanted electrodes, are certain to yield new capabilities. Any applications outside of medical intervention will be limited to adversaries with access to state-of-the-art research capabilities. The most likely types of applications will be in controls, such as of prosthetics, where output nerve signals can be coupled to a strong feedback mechanism in training.

- **Scenario 2**:

  Speculation: Brain-computer interfaces could be used for enhanced sensory input, information input, or control signals to enhance the performance of a combatant.

  State of the art: Modifying the input to the brain through external nerves is well-known, and in the case of sensory nerves has reasonably well-defined responses. Subjects require training to learn how to adapt to the signal inputs, and willing participants can adapt well. Unwitting subjects (rats) can be induced to adapt to simple control patterns, but technology for more sophisticated control of behavior or modification of emotions or thought patterns has limited specificity or efficacity (e.g., TMS or vagus nerve stimulation).

5 SUMMARY

Many research areas impact the broad topic of "human performance modification." These include learning, psychology, neurology, and pharmacology, as well as focused research in sleep and cognition, and development of prosthetics and treatments for spinal cord damage. As a result of many years of investment in developing a basic understanding neural function, as well as the development of new scientific tools, there is now an explosion of new applications and optimism concerning future developments. There are serious human needs that serve as strong motivation for these areas of research. However, there is the potential for abuses in carrying out such research, as well as serious concerns about where remediation leaves off and changing natural humanity begins. Such ethical considerations will appropriately limit the types of activities and applications in human performance modification that will be considered in the US military. In contrast, commercial activities, spontaneous human experimentation, and, most seriously, the activities of adversarial forces, will not likely be similarly constrained.

In addressing the question of potential threats that may arise from adversarial activities in human performance modification, the single most important factor is awareness, with the ability to assess the significance of the developing applications. This requires technically trained personnel, such as those now involved in evaluating and improving military nutrition, training and field stresses. In addition, it requires intelligence on activities in other cultures, and analysts with sufficient training in scientific evaluation to be able to evaluate reports and claims critically. Finally, it requires coordination with military analysts who can evaluate scenarios involving the potential applications of different types of performance modification.

Specific types of human performance modification are now beginning to be possible. Few represent a compelling immediate threat potential, but most are undergoing rapid development. As a result the long-term threat potential

can only be based on speculation concerning what emerging capabilities will result. In summation of the detailed presentations in the text, the areas in which such potential threats exist are:

1. **Sleep**: Military performance, and effective military force strength are severely impacted by the need for sleep. Sleep research is generating a growing awareness of sleep needs and sleep management. At present there is no clear path to a major breakthrough in this area, but if such a development occurs, possibly in combination with psychopharmaceutical developments (see # 3 below), it could seriously alter the balance of engagement.

2. **Training**: Increasing understanding of the fundamental neurological processes involved in learning can be used to develop more effective training regimens, as demonstrated in some cases for remediation of disabilities. It is possible to speculate on the threat potential if highly focused training were developed, possibly in combination with psychopharmaceuticals (see #3 below), that created specialized capabilities (possibly at the expense of loss of other normal abilities), or modified normal social inhibitions. However, even if possible, how such modifications would or could be implemented in realistic military scenarios needs analysis.

3. **Cognition**: New developments in psychopharmaceuticals target neural function more precisely. There is the distinct promise for new drugs that improve alertness and learning with fewer side affects than previous stimulants. The drugs have demonstrated effectiveness in remediating cognitive losses, and will certainly be tested and evaluated for cognitive enhancement. Threat potential could arise from adversarial use of such drugs to mitigate the effects of sleep deprivation, or in enhancing specialized training, along the lines discussed for items 1 and 2 above.

4. **Human-machine interface**: Indirect human control of machines using non-invasive monitoring of brain signals (such as EEG) is far inferior to normal human-machine interfaces based on physical controls. Non-invasive external influences on neural activity (such as TMS and DCS) have large individual variability and limited specificity in effect. Scenarios involving non-invasive "brain control" thus are unrealistic. Invasive interfaces require surgical intervention and thus represent far larger risks and costs in implementation. The most successful implementation of invasive interfaces has occurred in medical applications in which nerve signals are used as the mechanism for information transfer. Adversarial actions using this approach to implement enhanced, specialized sensory functions could be possible in limited form now, and with developing capability in the future. Such threat potential would be limited to adversaries with access to advanced medical technology.

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