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Neurotechnologies as weapons in national intelligence and defense – An overview

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Abstract

Advances in neuroscience and neurotechnology have necessitated discussions on the ways that such developments could be used as weapons in contexts of national security, intelligence, and defense. This paper defines the concept of neuroweapons, and elucidates operational issues associated with their use to aid informational and strategic intelligence, such as brain-machine interfaces to improve efficiency in data analysis. As well, exploration of neuropharmacologic, neuromicrobiological, and neurotoxic agents are discussed relevant to their utility in combat scenarios. The limitations of emerging neurotechnologies as weapons are addressed, as both regards practical and operational frameworks, and implications relevant to formulation of ethico-legal guidelines and governance of research, development and potential use.

Key words: neuroscience, neurotechnology, neuroweapons, neurosecurity, national defense, biotechnology, weaponry

Introduction

Advances in neuroscience have progressed rapidly over the last two decades. The field has become increasingly interdisciplinary, and has been a nexus for the development and use of a wide range of technological innovations (viz.- neurotechnology). While usually considered in medical contexts, many neurotechnologies may also be viably engaged as weapons. Such "neuroweapons" are obviously of great interest in and to national security, intelligence and defense (NSID) endeavors, given both the substantial threat that these technologies pose to the defense integrity of the US and its allies, and the viability of these approaches in the US NSID armamentarium. A 2008 report entitled *Emerging Cognitive Neuroscience and Related Technologies* by the ad-hoc Committee on Military and Intelligence Methodology for Emergent Neurophysiological and Cognitive/Neural Science Research in the Next Two Decades (National Research Council of the National Academy of Sciences (hereafter referred to as the 2008 NAS ad-hoc committee) (1) summarized the state of neuroscience as relevant to the 1) potential utility for defense and intelligence applications, 2) pace of progress, 3) present limitations, and 4) threat value of such science. In characterizing the challenges to advancing defense-oriented neurotechnologies — as well as maintaining the United States' international competitive edge — the committee noted that a significant problem was the "…amount of pseudoscientific information and journalistic oversimplification related to cognitive neuroscience." (1)

Given the relative nascence of neuroscience and much of neurotechnology, the development and use of neuroweapons discussed in this essay are incipient, and in some cases, the potential utility of these approaches is speculative. But any such speculation must acknowledge that neurotechnological progress in these areas is real, and therefore consideration of the potential trajectories that neurotechnologies-as-weapons might assume is both important and necessary. As well, such discussion must entail a pragmatic view of the capabilities and limitations

of these devices and techniques, and the potential pitfalls of — and caveats to — their use. Herein, we address 1) the possible ways that neurotechnologies can be utilized as weapons; 2) the NSID aims that might be advanced by neuroweapons; and 3) some of the consequences and/or implications of developing neurotechnologies toward these ends.

What is a neuroweapon?

A weapon is defined as "a means of contending against another " and "…something used to injure, defeat, or destroy" (2). Both definitions apply to neurotechnologies used as weapons in intelligence and/or defense scenarios. Neurotechnology can support intelligence activities by targeting information and technology infrastructures, to either enhance or deter accurate intelligence assessment, the ability to efficiently handle amassed, complex data, and human tactical or strategic efforts. The objectives for neuroweapons in a traditional defense context (e.g., combat) may be achieved by altering (i.e., either augmenting or degrading) functions of the nervous system, so as to affect cognitive, emotional and/or motor activity and capability (e.g., perception, judgment, morale, pain tolerance, or physical abilities and stamina). Many technologies (e.g., neurotropic drugs; interventional neurostimulatory devices) can be employed to produce these effects.

As implements that target, measure, interact with, or simulate nervous system function and processes, the use of neurotechnololgies as weapons are by no means a new innovation, per se. Historically, such weapons have included nerve gas, and various drugs. Weaponized gas has taken several forms: lachrymatory agents (a.k.a., tear gases), toxic irritants (e.g., phosgene, chlorine), vesicants (blistering agents; e.g., mustard gas), and paralytics (e.g., sarin). These may seem crude when compared to the capabilities of the more sophisticated approaches that can be used today — or in the near future (3). Pharmacololgic stimulants (e.g., amphetamines) and various ergogenics (e.g., anabolic steroids) have been used to augment combatant vigilance, and sedatives (e.g., barbiturates) have been employed to alter cognitive inhibition and facilitate cooperation during interrogation (3-7). Sensory stimuli have been applied as neuroweapons: some to directly transmit excessively intense amounts of energy to be transduced by a sensory modality (e.g., sonic weaponry to incapacitate the enemy), while others cause harm by exceeding the thresholds and limits of tolerable experience by acting at the level of conscious perception (e.g., prolonged flashing lights, irritating music, and sleep deprivation to decrease resistance to interrogation) (5). Even the distribution of emotionally-provocative propaganda as psychological warfare could be considered to be an indirect form of neuroweapon (8).

While such an expansive consideration may be important to evaluate the historicity, operational utility, and practical (and ethical) implications of neurotechnology-as-weapons, in this essay, we seek to provide a concise overview of neuroweapons, and therefore restrict discussion to applications of emergent technologies of cognitive neuroscience, computational neuroscience, neuropharmacology, neuromicrobiology, and neurotoxicology. The former approaches (e.g., cognitive and computational neuroscience; neuropharmacology) could be used for more indirect (yet still neurocentric) applications, including the enablement and/or enhancing of human efforts by simulating brain functions, and the classification and detection of human cognitive, emotional and motivational states to augment intelligence, counterintelligence, or human terrain deployment strategies. The latter methods (e.g., neuromicrobiology, neurotoxicology, as well as neuropharmacology) have potential utility in more combat-related or special operations' scenarios.

Contending against potential enemies: Neurotechnology within information infrastructures and intelligence strategy

Those neurotechnologies that enhance the capabilities of the intelligence community may be considered weapons in that they provide "…a means of contending against an other" (2). Certain neurotechnologies may be particularly well suited to affect performance in, and of the intelligence community. The tasks of both human analysts and the technologies they use are becoming evermore reciprocal and inter-dependent. Without technology to pre-process and sort large quantities of complicated information, human analysts could not obtain a cohesive picture from which to draw necessary inferences about the capabilities and intentions of (friendly, neutral or hostile) intelligence targets. Yet, information technology presently requires human programming and implementation of human-conceived models to parse the volume and types of information collected. Moreover, some information remains problematic to collect (e.g., attitudes and intentions of human subjects). Neurotechnologies that would facilitate and enhance these capabilities might decrease the fallibility of "human weak links" in the intelligence chain through the application of neurally-yoked, advanced computational

strategies (i.e., brain-machine, and machine-brain interfaces; BMI/MBI respectively) in the management and integration of massed data. Similarly, neurotechnologies can be developed to manage the increasingly significant problem of the sheer volume of cyber-based communications that has threatened intelligence systems with inundation. The widespread and inexpensive use of sophisticated communication technology (e.g., social media), and difficulty of allocating resources to gather intelligence-focal "signals" over evermore increasing, non-relevant "noise" has made more coherent collection and interpretation of intelligence information a priority (1, 9).

The principal neurotechnologies that can be used in these tasks are distributed human-machine systems that are either employed singularly, or linked to networked hierarchies of sophisticated BMIs, to mediate access to, and manipulation of signal detection, processing and/or integration. Neurotechnologic innovations that are capable of processing high volume, complex datasets are forms of physiomimetic computing hardware (1). Such hardware leverages analog, rather than digital components, with "a continuous set of values and a complex set of connections," based on an understanding of neural networks as more than mere binary switches. An analog circuit approach would address current "modeling and simulation challenges", be smaller and "…easy for the US — and its adversaries — to construct" (1). As well, given the analog nature of the magnetic fields used for real-time computing, a small, portable, physiomimetic computer of this type might be uniquely valuable for applications of high-density information processing (10-17).

Information systems could conceivably be conjoined so that neural mechanisms for assigning and/or detecting salience (i.e., processes involving cortical and limbic networks) may be either augmented or modeled into neurotechnologic devices for rapid and accurate detection of valid (i.e., signal vs. noise) information within visual (e.g., field sensor, satellite and UAV-obtained images) and/or auditory aspects (e.g., narratives, codes) of human (HUMINT) or signal intelligence (SIGINT). Formulating and testing credible hypotheses while monitoring large amounts of information could be accomplished by computational cognitive frameworks that are capable of both self-instruction (e.g., using the internet as a "training environment"), and learning from experience (e.g., via direct access to the operational environment). This articulates a form of artificial intelligence (AI) that functions to model — and embellish — human neural systems in cognition. The 2008 NAS ad-hoc committee identified such technology as a potential threat, but one that remains largely theoretical — at least at present (1). Such computational cognitive frameworks may "borrow" human capabilities, not by mimicking processes in the brain (which may not be sufficiently well understood to begin with), but by involving conceptual components of idealized neurally-modeled systems that are linked in ways that enable performance of similar — if not more rapid and advanced — neuro-cognitive functions. Moreover, neurally-coupled hybrid systems could be developed that link computational interfaces to human neuronal activity, so as to optimize Bayesian-like predispositions to certain types of stimuli (18). This would limit input datasets to more critical features, and thereby allow more efficient (i.e., rapid and accurate) detection, observation, orientation (and decisions) by the human user. Conjoinment and reciprocity could be used to enhance the feature-detection and intelligence capacities of both (the machine and human) systems.

Enhancement of neural and cognitive capabilities may be further achieved through some form(s) of cybernetics, broadly considered as a feed-back and feed-forward system that obtains iterative re-assessment and modification capacities through ongoing interactions between an agent and its environments (19). According to the classification scheme of Clynes and Kline (20), the use of human-machine interfaces can be regarded as a level 2 or level 3 cybernetic organism (viz.- a cyborg) in that it entails both natural and artificial systems that are functional, portable, and/or biologically integrated. Cybernetic and cyborg systems can be seen as sophisticated distributed human-machine networks, such as integrated software or robotic augmentations to human-controlled activity, that would fuse and coordinate the distinct cognitive advantages of humans and computers. As stated in the NAS ad-hoc committee report, these systems could assist "…advanced sensory grids, control and could control unmanned autonomous systems, advanced command posts and intelligence analyst workbenches, coordination of joint or coalition operations, logistics, and information assurance" with consequences that "enhance the cognitive or physical performance of war fighters and decision-makers or allow them to coordinate the actions of autonomous systems with much-improved effectiveness" (1). These systems would be of evident utility to multiple forms of intelligence acquisition and processing at both tactical and strategic levels.

Strategic intelligence

Strategic intelligence is defined as gathering and analyzing information regarding the capacities and intentions of foreign countries and actors; it may also encompass political intelligence, given that "…[political intelligence] is at once the most sought-after and the least reliable of the various types of intelligence. Because no one can predict with absolute certainty the effects of the political forces in a foreign country, analysts are reduced to making forecasts of alternatives based on what is known about political trends and patterns" (9). The complex dynamics of political forces that contribute to such predictive difficulty are due, in part, to the numerous and varied agents involved, all of whose actions are individually determined. Thus, understanding the bio-psychosocial factors that influence individual and group dynamics, and being able to detect these variables with high ecological validity (i.e., "in the field", under real-world conditions) is important to both descriptive/analytic and predictive intelligence approaches.

A combination of 1) advanced socio-cultural neuroscientific models of individual-group dynamics based upon theories of complexity adapted for use(s) in anthropology; 2) sufficient computing and BMI frameworks (perhaps as speculated above), and 3) certain forms of neuroimaging and magnetoencephalography to accurately detect the brain states and decision-biases of key or representative individuals might enable dramatically improved forecasting of behavior patterns that are influential to socio-political change. These forecasts could include the description of neuro-cognitive states of specific agents/actors, the propagation dynamics of an idea or cultural construct, and/or node-edge cognitive and behavioral interactions of individuals and cohorts- any and all of which might be viable to identify specific targets for subsequent manipulation (via other neuroweapons).

However, *intentions*, as opposed to corresponding cognitive and/or emotional states and their associated neuronal signatures, are difficult to detect using existing neurotechnologies. This affects and alters the modeling approaches that could — and should — be used to describe or predict individual or group activities. As well, it is important to consider the potential of technological interventions to alter events. Here, lessons may be garnered from experience with psychological warfare (6). Sometimes, techniques and tactics will induce unintended, if not frankly contrary effects and results. Given the overarching applications of neuro- and psychologically viable approaches, there is interest in neurotechnology to augment the role, capability, and effect(s) of psychological operations as a "force multiplier" in both political and military tactics. This trend began with the 1985 Department of Defense (DoD) psychological operations' (PSYOP) master plan and has been accelerated by the challenges posed by insurgencies in the present conflicts in Iraq and Afghanistan (21).

Such challenges emphasize the problems of cultural intelligence, and how these generate psychosocial obstacles to achieving tactical ends in the region. Tactical deficits may be related to the military approach to psychological-political warfare as being centered upon a "conflict of ideas, ideologies, and opinions" while not adequately emphasizing notions such as "cultural and political symbols, perceptions and emotions, behavior of individuals and groups under stress, and cohesion of organizations and alliances" (22). Even if we were aware of such variables, we might still be flummoxed in influencing "the minds and hearts" of enemy combatants, because of the failure to correctly define and predict which factors may affect aspects of psychological warfare (such as the severance or formation of alliances and collectives' reactions to the threat of integrity).

Thus, an appeal of neurotechnology is its (theoretical) potential for use in 1) defining substrates and mechanisms operative in culturally-relevant cognitions and behaviors, and 2) directly affecting perceptions, emotions, behaviors, and affiliative tendencies. The most obvious possibility is the use of neurotechnology to assess and affect cognitive capability, mood and/or motivation. Various forms of neuroimaging have been considered, as have the concomitant use of neurogenetics and neuroproteomic approaches in this regard. However, cognitive and emotional effects in individuals and across a population are complicated, and can often be unpredictable. Hence, a main criticism of neuroimaging is that although relatively valid and reliable in assessing individual mechanisms and substrates of cognition and emotion under controlled (i.e., experimental) situations, the ecological validity of such protocols is questionable, and thus neuroimaging may be of limited value in depicting more subtle cognitive-emotional, and motivational states, such as deception in "real-world" scenarios (23-24). Adding to this is that neuroimaging is not a subtle technique, and protocols for assessing cognitive-emotional variables would need to be explicitly concerned with the ways that the testing environment affects individuals being evaluated. Neurogenetics and neuroproteomics

could enable assessment of predispositional variables and even phenotypic characteristics that influence cognitions, emotions and behaviors, but these approaches are of only limited predictive value, given the non-linear relationship of genetics to both phenotype(s) and the ultimate expression of cognitive states and behavioral actions (25). Of course, today's limitations often represent the challenges and opportunities for tomorrow's technology, and ongoing work is dedicated to use of a more convergent scientific and technological paradigm to compensate for extant constraints and limitations, and create technologies that are effective and easily employed/deployed in operational settings (26).

Neuroweapons in combat scenarios

A considerably more imposing possibility is to "change minds and hearts" by altering the will or capacity to fight through the use of neuropharmacologic, neuromicrobiological and/or neurotoxic agents that 1) mitigate aggression and foster cognitions and emotions of affiliation or passivity; 2) incur morbidity, disability or suffering and in this way "neutralize" potential opponents, or 3) induce mortality. James Hughes (27) has identified 6 domains of neurocognitive function that can currently be pharmacologically manipulated; these are 1) memory, learning, cognitive speed; 2) alertness and impulse control; 3) mood, anxiety, and self-perception; 4) creativity; 5) trust, empathy, and decision-making; and 6) waking and sleeping. As well, movement and performance measures (e.g., speed, strength, stamina, motor learning, etc.), could also be enhanced or degraded (9).

Neurotropic drugs

As mentioned previously, the use of neuropharmacological agents to affect cognitive, emotional and behavioral abilities is certainly not novel (*vide supra*). However, an expanded capital of neuroscientific knowledge, namely the increased understanding of molecular and systems-based, structure-function relationships of the brain, has fortified depiction of substrates and mechanisms that are viable pharmacologic targets. Such knowledge, when coupled to advancements in pharmaceutical technology, has allowed discovery and development of neurotropic agents with greater specificity, potency, and bioavailabilty.

In general, drugs that have utility in combat and/or special operational settings include 1) cognitive and motoric stimulants such as the chain-substituted amphetamine, methylphenidate (28), and wakefulness-promoting agents (eugeroics) such as the novel dopaminergic reuptake blocker and histamine and orexin potentiating agent modafinil (29); 2) somnolent agents such as the barbiturates, benzodiazepines and certain opiates (30); 3) mood altering agents such as the azaspirone anxiolytics (e.g., buspirone; (30)), beta-adrenergic antagonists (e.g., propranolol, that has been considered for its effects in decreasing agitation and anxiety associated with traumatic events (30)), as well as dopamine and serotonin agonists (that at higher doses have been shown to induce fear, and psychotic symptoms including paranoia (31)); 4) "affiliative" agents such as the neurohormone oxytocin (32), and the substituted amphetamines (e.g., methylenedioxy methamphetamine, MDMA — "ecstasy" (33); and 5) convulsants, such as acetylcholine-agonists and gamma aminobutyric acid (GABA) receptor antagonists (34). The actions and effects of these categories of drugs are provided in Table 1.

While some of these agents can be used to enhance the neuro-cognitive and motor performance of (one's own) troops (e.g., low does of stimulants, mood altering drugs, etc), others have apparent utility against hostile forces (e.g., somnolent, psychotogenic, affiliative, and convulsant agents). Moreover, while a "weapon" is characteristically considered to be a tool used to incur injury, agents such as oxytocin and/or MDMA may actually reduce or prevent harm inflicted on an opponent by decreasing their desire to fight or making them more amenable to affiliation. These effects are wholly consistent with the more formal definition of a weapon, as "…a means of contending against another" (2). To paraphrase Kautilya, the person who becomes a friend is no longer an enemy (35). Yet, this too can be viewed as potentially harmful in that drug-induced effects upon cognition and emotion may alter the identity, autonomy, and free will of others, and in so doing, are exercises of "biopower" (36-38). Nevertheless, we opine that when attempting to balance benefits, risks and harms within contexts of *jus ad bello* and *jus in bellum*, such outcomes—while powerful—may need to be considered as less injurious than either more profound forms of neuro-psychiatric insult, or those produced by more "traditional" weaponry.

To be sure, the use of drugs to affect cognitive, emotional or behavioral function carries many potential risks of abuse (e.g., excessive doses or too-frequent use), misuse, unintended interactions with other drugs, foods and situations, and alterations in social behavior (27). Additionally, the effects of any drug depend on

Table 1. Neuropharmacologic Agents

Category	Type/Drugs	Principal Actions/Effects	Side effects/very high dose effects
Cognitive/motoric stimulants	CNS Stimulants (*e.g., amphetamines*[1]*, methylphenidate*[1]*, pemoline*[2])	Increase DA/NE turnover/release Increase arousal Increase attention Elevate mood Induce rebound depression and anxiety	Loss of appetite, insomnia, dizziness, agitation, increased heart rate, dry mouth, high-frequency tremor, or restlessness
	Eugeroics (*e.g., modafinil, adrafinil)*	Increase DA turnover Decrease DA reuptake Elevates hypothalamic histamine levels Potentiate action of orexin Wakefulness & decreased fatigue Increase arousal Increase attention Few autonomic side effects	Excitation or agitation, insomnia, anxiety, irritability, nervousness, aggressiveness, confusion, tremor, palpitations, sleep disturbances, or nausea
	Non-stimulant cognitive enhancers (ampakines[6] *e.g., ampalex, farampator, phenotropil*)	Potentiate AMPA receptor-mediated neurotransmission Increase attention Increase alertness No PNS stimulation Enhance learning and memory Increase tolerance to cold and stress	Possible headache, somnolence, nausea, or impaired episodic memory (Farampator)
	Other Nootropics (racetams[6] *e.g., piracetam, oxiracetam, aniracetam*)	Potentiate muscarinic ACh receptor activity Activate NMDA/glutamate co-localized with ACh receptors Non-specific increase in neuronal excitability (via AMPA and NMDA-receptor potentiation/ activation) Enhance learning and memory (nootropic) Anti-emetics Anti-spasmodics	CNS stimulation, excitation, depression, dizziness, sleep disturbances
	Monoamine reuptake inhibitors[1,2] (*e.g., buproprion*[2]*, atomoxetine, reboxetine, venlafaxine, mirtazapine*)	DA/NE reuptake inhibitors Antidepressant effects Decrease anxiety Increase concentration	Dry mouth, blurred vision, and dizziness, Buproprion causes seizures at high doses
Solmnolent and tranquilizing agents	Benzodiazepines[3] (*e.g., lorazepam, prazepam, clonazepam, oxazepam, diazepam, midalzolam, alprazolam*)	Increase GABA binding Increase neural inhibition Increase somnolence Decrease arousal Decrease reaction time/coordination Motoric lethargy Anterograde amnesic effects	Blurred vision, headache, confusion, depression, impaired coordination, trembling, weakness, memory loss
	Azaspirones[3] (*e.g., buspirone, gepirone*)	$5HT_{1A}$ receptor agonists Decrease NE activity Decrease arousal Decrease agitation Decrease anxiety	Dizziness, nausea, headache, nervousness, insomnia, lightheadedness
	Adrenergics[3] (*e.g., clonidine, guanfacine*)	Stimulate α-adrenergic receptors NE autoreceptor agonist Sedative effects Reduce heart rate Relax blood vessels	Dry mouth, dizziness, constipation

Table 1. Neuropharmacologic Agents, Continued

Category	Type/Drugs	Principal Actions/Effects	Side effects/very high dose effects
Solmnolent and tranquilizing agents (cont'd)	Barbiturates (*e.g., phenobarbitol, mephobarbitol, thiopental, amobarbital, secobarbital, pentobarbital*)	Bind to α subunit of $GABA_A$ receptors, Inhibit AMPA receptor-mediated glutamate activity High doses may inhibit neurotransmitter release Block ligand-gated cation channel receptors (nicotinic, glycine, $5\text{-}HT_3$ receptors) Decreased arousal Decreased concentration Impaired coordination Slurred speech Decreased anxiety	Potential for lethal overdose via respiratory depression
	Muscle relaxants (*e.g., carisprodol, cyclobenzaprine, metaxalone*)	CNS-acting muscle relaxers Anti-cholinergic Potentiation of NE $5HT_2$ antagonist; decrease descending 5-HT activity Analgesic effects Increases solmnolence	Potential anti-cholinergic effects, dry mouth, blurred vision, constipation, memory loss
	Imidazopirydine hypnotics (*e.g., zolpidem, zopiclone*)	Potentiate $GABA_A$ receptors Increase slow-wave sleep Facilitate sleep initiation (not maintenance) Anterograde amnesia	Hallucinations, sleep walking
	Antipsychotics/ Neuroleptics (dopamine antagonists *e.g., chlorpromazine, haloperidol, fluphenazine, thioridazine, loxapine, thiothixene, pimozide*)	Block D_2 DA receptors/ autoreceptors Decrease DA release Decrease agitation Increase sedation Hypothalamic effects on metabolism, body temperature, alertness, muscle tone, and hormone production	Sedation, blood pressure or heart rate changes, or dizziness, cognitive dulling
	Atypical antipsychotics[4] (*e.g., clozapine, risperidone, olanzapine*)	Block D_2 receptor types in limbic-system Decrease dopamine release Fewer extrapyramidal effects Some are anti-cholinergic (clozapine, perphenazine) May block $5\text{-}HT_{2A}$, α1 epinephrine, and H_1 histamine receptors	Tardive dyskenesia (uncontrollable writhing movements), neuroleptic malignant syndrome (hyperpyrexia)
	Anticonvulsants[3] (*e.g., gabapentin, pregablin*)	Anticonvulsant Anxiolytic Analgesic in neuralgia CNS depressants	Solmnolence, hypertonicity, abnormal gait, coordination, or movements, vision problems, confusion, eurphoria, and/or vivid dreams

Table 1. Neuropharmacologic Agents, Continued

Category	Type/Drugs	Principal Actions/Effects	Side effects/very high dose effects
Mood-altering agents	Other monoamine antagonists[5] (*e.g., reserpine, tetrabenazine*)	Prevent DA, NE, and 5-HT transport into synaptic release vescicles Deplete DA in presynaptic terminals Depress mood and motor activity Akasthesia, restlessness	Nausea and vomiting, severe depression, drowsiness, dizziness, and nightmares
	Beta-blockers[5] (*e.g., propranolol*)	β-adrenergic antagonists Decrease autonomic stress response Decrease performance anxiety Reduce posttraumatic agitation and anxiety	Dizziness/light-headedness, drowsiness, insomnia/dysomnia
	Dissociatives (*e.g., phencyclidine: PCP, ketamine*)	NMDA antagonists Alters monoamine release/reuptake Inhibit DA release in frontal cortex through presynaptic NMDA receptors (PCP) Increase DA release/ inhibit DA reuptake in limbic areas (PCP) Dissociative anesthesia (marked by catalepsy, amnesia, and analgesia) Induce/exacerbate psychosis (with euphoria/ dysphoria, paranoia, delirium, multisensory hallucinations) Ketamine induces anesthesia via σ- and μ-opioid receptors	Muscle weakness, ataxia, and loss of consciousness (ketamine), self-destructive or self-injurious behavior, impaired judgment
	Psychedelics (tryptamine alkaloids *e.g., ibogaine, yohimbine, psilocybin, LSD*)	5-HT_{2A} agonists Decrease 5-HT reuptake Loss of coordination Psychedelic/hallucinogenic effects σ_2 receptor, nicotinic receptor, NMDA antagonism	Dry mouth, nausea, and vomiting
	Dopamine agonists (*e.g., L-DOPA, tyramine, pargyline, benztropine, apomorphine* ropinerole*, bromocriptine**)	Inhibit DA reuptake/ breakdown, Increase DA release, or Act as DA receptor agonists* May induce psychosis	Induce nausea and vomiting Cause abnormal movements Increase compulsive behavior Enhance paranoia and/or fear response
Affiliative agents	Amphetamine derivatives (*e.g., 3,4-methylenedioxy-methamphetamine, MDMA* a.k.a., "ecstasy")	Increase net release of monoamine neurotransmitters (5-HT & NE > DA) Decrease 5-HT reuptake Increased wakefulness, endurance; postponement of fatigue and sleepiness Sense of euphoria and heightened well-being Sharpened sensory perception Greater sociability and extroversion Increased tolerance and desire for closeness to other people	Thermal dysregulation, muscle tension, headache, dry mouth, over-arousal (flight of ideas, insomnia, agitation, hyperactivity), panic attacks, delirium, depersonalization, mild hallucinations, or brief psychosis is possible, neurotoxic with chronic exposure
	Oxytocin[6]	Acts at CNS oxytocin receptors Evokes feelings of contentment, calmness, and security Reduces anxiety Increases trust and bonding Decreases fear Stimulates uterine contractions in pregnancy	Pro-social feelings, may sometimes include ethnocentrism, territoriality, and xenophobia

Table 1. Neuropharmacologic Agents, Continued

Category	Type/Drugs	Principal Actions/Effects	Side effects/very high dose effects
Epileptogenics	Inverse $GABA_A$ receptor agonists (non-volitile *e.g., DMCM, sarmazenil*; volitile *e.g., flurothyl*[6])	Act at benzodiadepine-binding site of $GABA_A$ receptors Decrease GABA-binding affinity of $GABA_A$ receptors Decrease frequency of chloride channel opening (to decrease inhibition) Convulsant, stimulant, and anxiogenic effects Inhalation of flurothyl elicits seizures Flurothyl mechanism not well-understood	
	Competitive $GABA_A$ antagonists (*e.g., gabazine, bucuculline*)	Bind competitively to $GABA_A$ receptors at GABA-binding site Reduce synaptic inhibition of neurons by decreasing chloride conductance	Convulsant effects
	Non-competitive $GABA_A$ antagonists (*e.g., picrotoxin bergamide, pentetrazol a.k.a., PTZ)*	PTZ also increases neuronal excitability by affecting cation currents via NMDA, 5-HT_{1A}, 5-HT_3, glycine receptors Anxiogenic Circulatory and respiratory stimulant	High doses cause convulsions
	Glycine Antagonists (*e.g., strychnine, tutin*)	Glycine receptor antagonist ACh receptor antagonist Initial effects of nervousness, restlessness, muscle twitching, neck stiffness give way to pupil dilation and convulsions of increasing severity	Highly toxic, convulsions, death by asphixiation
	Mixed GABA antagonist/ glutamate agonist (*e.g., cyclothiazide*)	Positive allosteric modulator of AMPA receptors Inhibit desensitization of AMPA receptors Potentiate glutamate currents Negative allosteric modulator of $GABA_A$ receptors Convulsant without neurotoxic effects	Seizures at higher doses
	Ionotropic glutamate receptor agonists (*e.g., kainic acid*)	Enhances glutamate effects through kainate receptors CNS stimulant Excitotoxic convulsant	Neuronal damage
	Muscarinic agonists (*e.g., pilocarpine*)	Non-selective muscarinic ACh receptor agonist Systemic injection leads to chronic seizures	Excessive sweating and salivation, bronchospasm and increased bronchial mucus secretion, vasodilation and bradycardia
	Non-specific cholinergic agonist (e.g., *physostigmine*)	Acetylcholinesterase inhibitor Increases synaptic ACh levels Indirectly stimulates nicotinic and muscarinic receptors	Convulsant at high doses
	Local anesthetics (e.g., *lidocaine*, *prilocaine*)	Block fast voltage gated sodium channels Inhibit neuronal firing Moderate systemic exposure causes CNS excitation, symptoms of nervousness, dizziness, blurred vision, tinnitus and tremor Seizures followed by depression	With higher doses, drowsiness, loss of consciousness, respiratory depression and complete apnea

[1] also elevates mood or antidepressant effects; potential as mood-altering agent(s)
[2] also lowers seizure thresholds; potential epileptogenic effects, especially at high doses
[3] also anxiolytic; potential mood-altering agent(s)
[4] also decreases agitation/psychosis and/or antidepressant effects; potential as mood-altering agent(s)
[5] significant sedation side effects; potential as solmnolentic agent(s)
[6] mechanism not fully understood or effects inconclusively established at this time

Note: ACh: acetylcholine; CNS: central nervous system; DA: dopamine; GABA: gamma amino butyric acid; 5-HT: 5-hydroxytryptamine (serotonin); NE: norepinephrine; NMDA: n-methyl D-aspartate

an individual's particular combination of genes, environment, phenotype, and the presence or absence of both physiological and psychopathological traits, and these can vary widely within a given population. Despite the relatively small size of the military, considerable diversity still exists in the aforementioned characteristics, and this would need to be accounted for, as would any variations in those populations in which the use of neurotropic agents is being considered.

Thus, it is probable that any neurotropic agent would produce variable responses and effect(s) in a population reflective of individual geno- and phenotypes, as well as biological variation in given individuals over time. This could incur an increased likelihood of unanticipated effects; therefore, it is important that pharmaceutical research, development, testing and evaluation (RDTE) of such agents engage the time and resources required to maximize desirable drug actions and effects based upon individual and group geno- and phenotypes, and assess potentially adverse and/or unwanted side-effects. Of course, adverse effects could also be exploited for use on an enemy population. In light of this, drug design would require resources necessary for evaluation and measurement of geno- and phenotypic characteristics that could be optimized to selectively employ particular drugs within a population. By targeting these characteristics, it would be possible to mass deliver agents and still achieve some significant measure of individualized effect(s). Current efforts in "personalized medicine" may afford steps toward realizing these possibilities (39-40). As well, certain physiochemical obstacles to delivery have been overcome by the use of nano-neurotechnologies that have allowed molecular conjugation or encapsulation of ligands, ligand precursors, and biosynthetic enzymes capable of crossing the blood-brain and blood-cerebrospinal fluid (CSF) barriers, and thus permitting greater access to, and higher bioavailability within the brain (1).

Neuromicrobiological agents

A number of microbiological agents directly target or indirectly affect the central nervous system (CNS), and these are certainly employable as neuroweapons (1,10). Of particular note are 1) the viral encephalitides, such as the *Alphavirus* genus of the Togaviridae family that cause Venezuelan, eastern and western equine encephalitis (41); 2) the anaerobic bacterium *Clostridium botulinium*, the seven strains of which produce specific neurotoxins (42); and 3) the sporulating bacillus, *B. anthracis* that causes anthrax (42). (See Table 2)

Here too, use of nanotechnology to preserve stable forms of pathogenic agents could be important for producing more durable aerosolized neurobioweapons (43). While these agents are capable of inducing large-scale infections in a given population, such mass casualty effects may not be required or desired. Instead, using these agents in more punctate approaches might be of greater advantage. Such techniques include: 1) inducing a small number of representative cases (with high morbidity and/or mortality) that could incur mass public reaction (e.g., panic and/or paranoia) and impact upon public health resources – inclusive of a strained public-governmental fiduciary; 2) targeting specific combatants to incur health-related effects upon operational infrastructures; or 3) "in close" scenarios in which particular individuals are targeted for effect in order to incur more broadly based manifestations and consequences.

Neurotoxins

Of the aforementioned scenarios in which neuroweapons could be leveraged, the latter two are prime for the use of organic neurotoxins. These agents are extracts or derivatives of peptides found in mollusks (i.e., conotoxins), puffer fish and newts (i.e., tetrodotoxin) dinoflagellate algae (i.e., saxitoxin), blue ringed octopus (i.e., maculotoxin), and species of cobra (i.e., naja toxins). As depicted in Table 3, all are potent paralytics, acting through mechanisms of ionic blockade (e.g., acetylcholine receptor agonism or antagonism; or direct inhibition of sodium, calcium or potassium channels) in the peripheral nervous system and/or at the neuromuscular junction (NMJ) (44), to induce spastic or flaccid paralysis and cardio-respiratory failure. Being peptides, the stability of these agents vary, but can be enhanced through chemical alterations such as structural cyclization, disulfide bridge modification, and substitution of various residues (45), thereby increasing their utility.

In all cases, paralysis occurs rapidly after introduction of a small dose of the agent, and the victim remains conscious until overcome by shock and/or respiratory arrest. As well, except for the naja toxins (for which there are a number of species-specific antivenins, that each differ in effectiveness), antidotes are not available, and rapid triage for cardio-respiratory support is required to prevent mortality (although the effects of tetrodotoxin can be mitigated with edrophonium (46).

Table 2. Neuromicrobiologic Agents

Category	Agent	Action	Effects
Viral encephalitides	Togaviridae *Alphavirus* (e.g., Venezuelan, eastern, and western, and equine encephalitis viruses Bunyaviridae *Orthobunyavirus* (e.g., La Crosse virus (LCV) and James Canyon virus (JCV) variants of California encephalitis virus) Flaviviridae *flavivirus* (e.g., Powassan virus)	Arthropod vectors (mosquitoes, ticks) Single-stranded RNA genomes Invade the brain via vascular endothelial cells Replicates in neurons of cerebral cortex Causes neuronal necrosis	Encephalitis: headache, nausea, vomiting, lethargy, seizures, coma, and possible paralysis or focal signs of neuropathy. LCV: primarily children; <1% mortality; but most have persistent neurological sequelae (e.g., recurrent seizures, partial to full hemiparalysis; cognitive and neurobehavioral abnormalities)
Microbial encephalitides	Amoebic parasite (e.g., trophozoites of *Naegleria fowleri*)	Amoeba penetrate nasal mucosa after insufflation or ingestion of infected water Invades CNS via olfactory nerve. Progressively necrotizes brain tissue	Primary amoebic meningoencephalitis (PAME) Progressive meningitis resulting in encephalitis. Death from respiratory failure consequential to inflammation and/or necrotization of the brainstem Mortality in 2 -4 weeks
	Protozoan parasite (e.g., *Toxoplasma gondii)*	Feline hosts Zoonotic transmission via human contact or insufflation of fecal matter. Ingested; becomes active in immunocompromised host Encodes the DA synthetic enzyme tyrosine hydroxylase Increases CNS DA levels Induces polyfocal neuroinflammation	Behavioral changes resembling those of dopamine reuptake inhibitor type antidepressants and stimulants. Loss of impulse control; agitation, confusion. Encephalitis

Table 2. Neuromicrobiologic Agents, Continued

Category	Agent	Action	Effects
Bacterial toxigenics	*Bacillus anthracis* (i.e., anthrax toxin)	Bacterial spores are inhaled and uptaken by macrophages Spores become active bacilli and rupture macrophages, releasing bacteria into bloodstream, where the anthrax toxin is released Anthrax toxin enables bacteria to evade the immune system, proliferate, and ultimately cause polyfocal effects	Anthracic meningitis Inhibition of protective immune responses Cell lysis and destruction Bleeding and death
	Clostridium botulinum (i.e., Botulinum toxin) *(*also*, C. butyricum C. baratii C. argentinense)*	Decreased acetylcholine release. Decreased neuromuscular transmission	Induces flaccid paralysis and cardio-respiratory failure
	Several genera of *cyanobacteria (e.g., anabaena, aphanizomenon oscillatoria, microcystis, planktothrix, raphidiopsis, arthrospira,cylindrospermum, phormidium)* (i.e., anatoxin-α)	Stimulates nicotinic ACh receptors Mimics ACh causing irreversible stimulation of NMJ	Permanent contraction of muscles Loss of coordination, twitching, convulsions and rapid death by respiratory paralysis
	Gambierdiscus toxicus (i.e., ciguatoxin)	Lowers the threshold for activating voltage-gated sodium channels	Causes headache, muscle aches, weakness, dizziness, itching. nightmares, and/or hallucinations. Causes parasthesias (e.g., sensation of burning or "pins-and-needles", reversal of hot and cold temperature sensation, or unusual tastes) Very low mortality; recovery within 1 month.

Note: ACh: acetylcholine; DA: dopamine; NMJ: neuromuscular junction

Table 3. Organic Neurotoxic Agents

Origin	Agent	Mechanism
Marine cone snails (genus *Conus*, e.g., *Conus geographus*)	σ-conotoxin	Inhibits the inactivation of voltage-dependent sodium channels; prolonged opening.
	ϰ-conotoxin	Inhibits the inactivation of voltage-dependent sodium channels; prolonged opening.
	μ-conotoxin	Inhibits voltage-dependent sodium channels in muscles.
	ω-conotoxin	Inhibits N-type voltage-dependent calcium channels.
Symbiotic bacteria found in rough-skinned newts, pufferfish and procupinefish (e.g., *Pseudoalteromonas tetraodonis*, certain species of *Pseudomonas* and *Vibrio*)	tetrodotoxin	Prevents action potential firing in neurons Binds near the pore and blocks voltage-gated fast sodium channels on presynaptic terminals
Symbiotic bacteria found in blue-ringed octopus (*Hapalochlaena maculosa*)	Maculotoxin (a venomous form of tetrodotoxin)	Presynaptic sodium channel pore blockade Inhibition of action potential firing
Shellfish/molluscs (e.g., *Saxidomus giganteus* contaminated by algal blooms ("red tides") e.g., *Alexandriu catenella*), and Pufferfish	Saxitoxin (e.g., saxitoxin, gonyautoxin, neosaxitoxin)	Selective pore blocker of neuronal voltage-gated sodium channels Water soluble and dispersible by aerosols Inhalation causes death within minutes
Cobra snake (Genus *Naja*)	Naja toxins (e.g., α-cobratoxin)	Block nicotinic ACh receptors at NMJ Also selective antagonist to α7-nicotinic ACh receptors in the brain
Krait snakes (*Bungarus multicinctus)*	Bungarotoxins (e.g., α-bungarotoxin)	Irreversible and competitive binding to NMJ nicotinic ACh receptors Also selective antagonist to α7-nicotinic ACh receptors in the brain
Mamba snakes (*Dendroapsis*)	Dendrotoxins (e.g., α-dendrotoxin, σ-dendrotoxin)	Block voltage-gated (A-type) potassium channels at nodes of Ranvier in motor neurons Prolong duration action potentials Increase ACh release at NMJ
Australian taipan snakes (*Oxyuranus scutellatus*)	Taipoxin	Induced increasing blockade of presynaptic ACh release from motor neurons

Note: ACh: acetylcholine; NMJ: neuromuscular junction

Practical considerations, limitations and preparations

The use of such neuroweapons, especially if apparent, is unlikely to result in lasting peace. Yet, the distribution of a neurotropic drug or neuropathological agent throughout a population could create a societal burden that significantly impacts the means, economic resources, and/or motivations to fight. But there is also the risk of a number of "spillover effects". First, given the environment(s) in which most current warfare is conducted, it would be nearly impossible to completely protect a civilian population from the effects of neuroweapons. If the agent has a known antidote or may be inoculated against, these might be relatively easy to counter—but this would depend upon the integrity of the public health infrastructure of the town or country in which the agents are employed (and/or the capability of military forces to provide medical assistance to those civilians that are affected). Second, if an antidote is not available, then there is risk of both serious collateral injury to the civilian population, and injury to one's own troops should they be exposed to the agent. Third, there is risk to much broader populations if stocks of the agent were purloined from secure storage, or should a neuromicrobiological agent mutate while being employed (1).

Evidently, these considerations prompt ethical and legal concerns that must be addressed – and resolved – through the formulation of guidelines and policies. A complete discussion of the ethico-legal and social issues arising from the use of neuroscience and technology in national security and defense agendas is beyond the scope of this essay (for a more detailed review of this topic, see the *American Journal of Bioethics-Neuroscience*, April-June 2010, volume 1, number 2). Suffice it to state that any and all use of neuroscience and neurotechnology in this regard mandates rigorous ethical analysis and discourse that is inclusive of the research, academic, political and public communities.

While the use of neurotechnology in national security, intelligence and defense applications may be relatively new, the concept of using psychological science to develop weaponry is not. In some ways, it may be as difficult to distinguish between neurotechnological and psychological warfare as it is to discriminate structure from function as relates to brain and mind. "Changing minds and hearts" may not be a task that is best addressed by neurotechnologies as weapons. Instead, cultural sensitivity and effective communication might be a more desirable approach (1, 47-48).

Still, neurotechnology will be evermore viable in translating the nuances of social cognition and behaviors, and thus gaining a deeper understanding as to why certain principles or violations are more or less likely to induce violence and/or strong opposition. Neurotechnology could— and likely will— play an increasingly larger role in exploring the relationships between culture and neuropsychological dynamics in and between populations.

But, here we pose a caveat: Ignoring unresolved ambiguities surrounding issues of the "brain~mind" and "reductionist/antireductionist" debate (i.e., as connoted by the "neuro" prefix) when employing scientific evidence as rationale for employing neurotechnologies as weapons may lead to erroneous conclusions that may profoundly affect the intelligence and defense community – and the public. An example is the current interest in using functional neuroimaging (fMRI) for detecting deception (1). The validity of this approach depends on the accuracy with which such technologies can detect psychological states relevant to deception (such as anxiety versus something more abstract, e.g., cognitive dissonance). How science portrays the relationship between patterns that may be detected by neuroimaging, and what those patterns actually represent depends upon (neuroscientific) interpretation of the validity of the technology (to actually do what it is intended), and, in light of this, the meaning of data and information, as constituting viable knowledge (24,49-50).

An illustration of how (mis-)conceptions of causal relationships of the brain and cognition can constitute a rationale for employing technologies or tactics is reflected by the following quote, from the May 4, 2009 issue of Newsweek. In context, the speaker is asking the contractor who will replace him about a given approach to interrogation:

> *"…I asked [the contractor] if he'd ever interrogated anyone, and he said 'no, but that didn't matter', the contractor shot back, 'Science is science. This is a behavioral issue.' He told me he's '…a psychologist and… knows how the human mind works'" (51).*

This is relevant to the use of neurotechnology as it reflects a social tendency to concretize contingent neuroscientific understanding as "truth". To be sure, knowledge in neuroscience remains a work-in-progress, and thus, so does any definition of what is real, true (i.e., based in fact), valid, and possible as regards the applications and use(s) of neurotechnology. Still, neurotechnology can be used to create weapons that may have an unprecedented capacity

to alter the cognitions, emotions, beliefs, and behaviors of individuals, and groups – if not societies. Thus, the potential "power" of neurotechnology as weaponry lies in the ability to assess, access and change aspects of a definable "self". As with any weapons, they pose threats to autonomy and free will, and can do so to an extent that psychological weapons alone could not.

It is foolhardy to think that the technological trend that compels the use of neurotechnology as weapons will be impeded merely by considerations of 1) the burdens and risks that might arise as science advances ever deeper into the frontiers of the unknown; 2) the potential harms that such advances could intentionally and/or unintentionally incur, and 3) the ethico-legal and social issues instantiated by both the positive and negative effects and implications of these advances. This is because a strong driving (or "pushing") force of both science and technology is the human desire(s) for knowledge and control. At the same time, environmental events, market values, and socio-political agendas create a "pulling force" for technological progress, and can dictate direction(s) for its use. Both former and latter issues are important to national security and defense. In the first case, the use of contingent knowledge could evoke unforeseen consequences that impact public safety, and the power conferred by scientific and technological capability could be used to leverage great power. In the second case, the intentional use of these technologies by individual agents or groups in ways that are hostile to the national interests of the US and its allies could incur profound public threats.

Thus, a simple precautionary principle in which risk: benefit ratios determine the trajectory and pace of technological advancement is not tenable on an international level, as there is the real possibility – if not probability – that insurgent nations and/or groups could fund and covertly conduct RDTE of neuroweapons, beyond the auspices and influence of US (and/or UN) guidelines and policies. Instead, we argue for a process that entails some measure of precaution, together with significant preparedness. Such preparedness requires knowledge of 1) what technological accomplishments can be achieved (given the incentives and resources afforded); 2) whether such work is being prepared and/or undertaken; 3) groups involved in such work; 4) overt and/or covert intention(s) and purposes; 5) what possible scenarios, effects and consequences could arise from various levels of technological progress, and 6) what measures can and should be taken to counter threats imposed by such progress and its effects (52). For this approach to work, surveillance (i.e., intelligence) is necessary, and thus the development and use of many of the aforementioned neurotechnological developments becomes increasingly important. Although international governance of neurotechnological RDTE may be difficult, what can be governed and regulated are the ways in which neuroscientific and neurotechnological RDTE efforts are conducted and employed by agencies of the US and its allies. In this regard, ethical questions need to be prudently addressed and balanced with the interests of public (viz. - national) security and protection.

Conclusion

In an ideal world, science and technology would never be employed for harmful ends; but we should not be naïve and succumb to the dichotomy of ought versus is. Neuroscience can – and will – be engaged to effect outcomes relevant to NSID operations by countries and non-state entities to achieve goals that are contrary to the interests and public welfare of the United States and its allies. As history has shown, a dismissive posture that fails to acknowledge the reality of threat increases the probability of being susceptible to its harms. In an open society, it is the responsibility of the government to protect the polis. Hence, there is a duty to establish proactive, defensive knowledge of these scientific and technological capabilities and the vulnerabilities that they exploit, to recognize how neuroscience and neurotechnology could be used to wage hostile acts, and to develop potential countermeasures to respond appropriately. But a meaningful stance of preparedness also mandates rigorous analyses and address of the ethico-legal and social issues that such use – and/or misuse – of neuroscience and neurotechnology generate, and guidelines and policies must be formulated to effectively direct and govern the scope and conduct of research and its applications in this area. Our group remains dedicated to this effort and approach.

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Disclaimer

The views expressed reflect those of the authors and not necessarily those of their respective institutions.

Competing interests

The author(s) declare that they have no competing interests.

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