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Polioencephalitis and the Brain Fatigue Generator Model of Post-Viral Fatigue Syndromes.

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ABSTRACT

Fatigue is the most commonly reported and most debilitating Post-Polio Sequelae (PPS) affecting millions of polio survivors world-wide. Post- polio fatigue is associated with: 1) subjective reports of difficulty with attention, cognition, word-finding and maintaining wakefulness; 2) clinically significant deficits on neuropsychological tests of information processing speed and attention; 3) gray and white matter hyperintensities in the reticular activating system on magnetic resonance imaging of the brain; 4) neuroendocrine evidence of impaired activation of the HPA axis. Many of these findings are identical to those

documented following a variety of viral encephalitides, including acute poliovirus infection, lethargic encephalitis, Iceland Disease, myalgic encephalomyelitis, and, most recently, Chronic Fatigue Syndrome. The clinical, historic, neuropsychologic, neuroanatomic and physiologic parallels between poliovirus infection, post-polio fatigue and post-viral fatigue syndromes (PVFS) will be explored in an attempt to describe the pathophysiology of PVFS. The disinhibition of a putative Brain Fatigue Generator will be implicated as a cause of the subjective symptoms and objective signs that accompany PVFS. The results of a pilot placebo-controlled study of a dopamine 2 receptor agonist to treat post-polio fatigue will also be described.

Fatigue is the most commonly reported, most debilitating and least studied Post-Polio Sequelae (PPS) affecting millions of polio survivors throughout the world. In two national surveys of American polio survivors, 91% reported new or increased fatigue, 41% reported fatigue significantly interfering with performing or completing work and 25% reported fatigue interfering with self-care activities. 1 Fatigue was reported to be triggered or exacerbated by physical overexertion in 92% and by emotional stress in 61%.

Importantly, polio survivors differentiate between the physical tiredness and decreased endurance they associate with new muscles weakness, and a "brain fatigue" that is characterized by problems with attention and cognition.

Between 70% and 96% of American polio survivors reported that fatigue was accompanied by problems with concentration, memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% percent reporting at least moderate to severe difficulty with these problems. 2

These reports of late-onset "brain fatigue" are reminiscent of the persistent drowsiness, fatigue and fleeting attention that frequently followed the acute poliovirus infection. Clinical reports written during the polio epidemics documented "drowsiness," lethargy, apathy, slowing of the EEG, prolonged somnolence, "fatigability and fleeting attention" for months after the acute episode of paralytic and even non-paralytic polio. 3-8 Such symptoms should have been expected since poliovirus produced an encephalitis, whether paralysis was present or not, consistently and often severely damaging brain areas responsible for cortical activation - the midbrain reticular formation, thalamus, locus ceruleus, posterior and paraventricular hypothalamus (i.e., the reticular activating system (RAS)) - and for directed attention, i.e., the putamen, globus pallidus and the substantia nigra. 5-17 (Fig. 1)

POST-POLIO FATIGUE AND POST-VIRAL FATIGUE SYNDROMES

Both acute and late-onset post-polio fatigue are also reminiscent of Myalgic Encephalomyelitis (ME), Iceland Disease and Chronic Fatigue Syndrome (CFS). 18-19 There

are a number of clinical, historical, anatomical and physiological parallels between polio and these putative post-viral fatigue syndromes (PVFS).

Myalgic Encephalomyelitis. Between 1934 and 1954 there were over a dozen outbreaks of a syndrome that was at first diagnosed as poliomyelitis, then as "abortive" or "atypical" poliomyelitis and finally as Myalgic Encephalomyelitis (ME). 18 Like poliomyelitis, initial symptoms of ME included headache, neck pain, low-grade fever and myalgia that were often followed by paresis. Patients also demonstrated hypersomnolence, slowing of the EEG and "conspicuous changes in their levels of concentration" that persisted for months after the acute illness. 18 Unlike poliomyelitis, there were frequent complaints of numbness or parasthesias, usually no respiratory involvement, infrequent paralysis or muscle atrophy and almost invariably no fatalities. Also unlike poliomyelitis, recovery from the acute symptoms of ME sometimes required months and most patients were left with a marked "exhaustion and fatiguability" that were "always made worse by exercise [and] emotional stress."18-20 Patients continued to demonstrate fatigue, hypersomnolence and impaired concentration and reported "an inordinate desire to sleep," anomia, that they were "not as quick or incisive in thought as before, [had] a decreased ability to learn and a decline in their short-term memoryÓ for years after the acute episode. 18

Despite the differences between poliomyelitis and ME, and

the fact that poliovirus was never isolated from ME patients, some association with the poliovirus was suggested. Of the more than one dozen ME outbreaks before the introduction of the Salk vaccine, nine occurred during or immediately after outbreaks of polio and several involved hospital staff who cared for polio patients. 21-28

Iceland Disease. The PVFS epidemic most intimately linked with polio occurred in Akureyri, Iceland in 1948. Following the diagnosis of two unequivocal cases of poliomyelitis, patients began presenting with fever, myalgia and paresis and were at first diagnosed as having poliomyelitis. 29 This diagnosis was discarded as patients reported additional symptoms atypical of polio, including parasthesias, numbness, "nervousness" and "general tiredness" both acutely and for months after the acute episode. Six years after the original infection, 72% complained of "nervousness and general tirednessÓ while 21% reported "loss of memory." As in ME, poliovirus was never isolated from any of these patients.

Two alternatives were suggested for the cause of this constellation of symptoms that Sigurdsson called Akureyri Disease but has been more commonly referred to as Iceland Disease (ID): "Either a strain of poliomyelitis virus with unusual pathologic properties and of low virulence was responsible for this epidemic or . . . some unknown neurotropic virus has been present." 30 Support for an "unusual" poliovirus as the cause came in 1955 with an

"extensive epidemic" of poliomyelitis, caused by Type I poliovirus, that coincided with and was followed by outbreaks of ID. 31 Remarkably, two Icelandic cities in which ID outbreaks were reported in 1955, as well as the area affected by the 1948 Akureyri Disease epidemic, were untouched by poliomyelitis. None of the children tested in the two new ID-affected cities, and only 13% of the children in Akureyri, showed antibodies to Type I poliovirus as opposed to 86% of the children tested in the polio epidemic areas. Further, following poliovirus immunization, children in one of the ID- affected cities demonstrated antibody titres to Type II and Type III poliovirus that were four and twenty-five times higher, respectively, than titers in a city where ID had not been reported. The authors concluded that Type I poliovirus was not related to the occurrence of ID but that inhabitants of the ID-affected areas had previously been exposed to an agent immunologically similar to Type III poliovirus.

Chronic Fatigue Syndrome (CFS). Like post-polio fatigue, ME, and ID, CFS is associated with complaints of chronic fatigue, triggered or exacerbated by physical exertion and emotional stress, that have been associated with impaired concentration, memory and word finding ability, and an excess of irregular slow wave activity on EEG. cf. 3; 2, 32-36

Subjective difficulties with attention in CFS patients and polio survivors with fatigue have been corroborated by the documentation of clinical abnormalities on

neuropsychological testing. CFS patients and polio survivors with severe fatigue demonstrated clinically significant impairments of attention and information processing speed. 17, 37-40 In spite of these marked impairments of attention, polio survivors and CFS patients in several studies have been shown to be within the high normal on measures of higher-level cognitive processes and I.Q. 1,33,40 Further, despite the high frequency of subjective complaints of memory impairment in CFS patients and in 87% of polio survivors reporting fatigue, verbal memory has been shown to be intact on testing in both groups. 2, 38-40

In some studies, magnetic resonance imaging (MRI) of the brain has also shown similarities between CFS and post-polio fatigue. Areas of hyperintense signal in gray and white matter were imaged in 55% of polio survivors reporting at least moderate daily fatigue but were not imaged in any subjects reporting mild fatigue. 42 Small discrete or multiple punctate areas of HS were imaged in the putamen, the rostral reticular formation, centrum semiovale, periventricular and deep white matter. The presence of HS was significantly correlated with the severity of fatigue, subjective difficulty with thinking clearly, mind wandering, attention, recent memory and concentration, but not with depressive symptoms or difficulty sleeping. These areas of HS were interpreted as evidence of poliovirus damage to the basal ganglia, RAS and its associated corticofugal white matter tracts. 2 This conclusion is supported by a recent case of poliomyelitis, in which HS in the midbrain and medulla

on antemortem MRI corresponded with histopathological findings of necrosis in the substantia nigra and reticular formation on autopsy. 43

Periventricular and deep white (but not gray) matter HS have also been imaged in 27% to 100% of CFS patients. 44-45 White matter HS imaged in both demented and non-demented elderly adults have also been associated with impairments of attention and information processing speed similar to those documented in CFS patients and polio survivors. 46; cf. 52

Neuroendocrine data also show similarities between CFS and post- polio fatigue. 17 Plasma ACTH was significantly elevated and outside of the normal range following an overnight fast in polio survivors reporting mild daily fatigue (28.5 ± 17.7 ng/ml) but not in those reporting high (>moderate) fatigue (19.7 ± 10.7 ng/ml) ($t=2.02$; $p<0.05$). Plasma ACTH was also significantly negatively correlated with the frequency of problems with recent memory, word finding and muscle weakness, the severity of daily fatigue, recent memory and staying awake during the day, but not with the severity of depressive symptoms. Plasma cortisol levels were neither elevated nor different between subjects reporting mild (14.8 ± 5.7 ug/dl) and high daily fatigue (12.6 ± 5.2 ug/dl).

These data suggest that the HPA axis response to stress is blunted in polio survivors reporting fatigue. Decreased HPA activity has already been documented in patients with CFS

and the reduced secretion of "activating" peptides such as CRH and ACTH has been implicated in its pathophysiology. 53-54

POLIOENCEPHALITIS AS A PROTOTYPE FOR PVFS

These data suggest that poliovirus may be the prototype for a chronic fatigue-producing agent since it routinely and often preferentially damaged areas responsible for brain activation and attention and has been so often associated during this century with symptoms of acute and chronic fatigue. Certainly, poliovirus is not the only agent for which the brain's activating system is its "favourite location." Both gray and white matter lesions have been demonstrated with a variety of viral encephalitides whose symptoms include markedly impaired cortical activation, e.g., St. Louis, Japanese B, Equine and Australian X encephalitis and Central European Encephalomyelitis. 55-56 Still other agents (e.g., Coxsackie, echo and herpes viruses) have been associated with symptoms of chronic fatigue. 18-20 And, although there is no convincing clinical or immunological evidence that post-polio fatigue or CFS is caused by a persistent poliovirus infection, only poliovirus has been directly or indirectly associated so often throughout this century with acute and chronic impairment of cortical activation, decreased attention and symptoms of fatigue. 57-58 (Explanations for the recrudescence, de novo and stress-induced appearance of post-polio fatigue are presented elsewhere. 2,17)

POLIOENCEPHALITIS AND THE BRAIN FATIGUE GENERATOR

The findings presented above describe an integral relationship between polioencephalitis, decreased cortical activation and impaired attention. However, impaired attention is not fatigueÕs only symptom. Even more disabling is the "visceral" experience of fatigue: feelings of exhaustion, "passivity and an aversion to continued effort" that generate an antipathy toward both mental and physical activity. 59,60 However unpleasant and disabling these feelings are in humans, passivity and aversion to activity have clear survival value, especially in animals without conscious awareness that attention and information processing speed are impaired. An animal that continues to explore its environment even though its attention is impaired would be less able to direct and sustain attention on the goal of its exploration (e.g., searching for food) and would waste already diminishing energy stores. More importantly, impaired attention and information processing speed could also render an animal unaware of or slow to respond to dangers in its environment (e.g., a predator stalking the animal in search of its food). Thus, there would be survival value in a "Brain Fatigue Generator" that monitors cortical activation and biases the organism toward cessation of motor behavior and promotes sleep when attention and information processing ability are impaired. To explain pathological fatigue, some agent would have to impair the putative Brain Fatigue Generator by damaging brain areas

responsible not only for cortical activation and attention, but also for behavioral activation and intentioned movement.

Putamen as Cortical Monitor. The lenticular nuclei are uniquely situated to act as the Brain Fatigue Generator (BFG), which monitors the level of cortical activation, stops an organism from moving and promotes sleep when its attention is inadequate to allow efficient and safe motor behavior. (Fig. 2) All cortical areas project to the dorsal striatum, especially the putamen which receives 33% of its innervation from the cortex. 61 The dorsal striatum is said to Òaccumulate samples of ongoing cortical projected activityÓ via glutaminergic cortical efferents that synapse with the distal dendritic spines of putamenal GABAergic medium spiny neurons (MSN). 62-66 The putamen also sends excitatory efferents to the descending reticular formation (dRF) that increase tonic motor unit activity and muscle tone. 61,65,67 Muscle tone is important not only in preparing an animal for movement, but also in activating the cortex via muscle spindle afferents that stimulate the ascending reticular formation (aRF). 61,68,69 Decreased muscle tone, induced by curarization, has been shown to produce cortical synchronization and "drowsiness" and even induce a level of anesthesia sufficient to perform surgery. 70-72

Animals with lesions of the putamen demonstrate "difficulty transferring attention from one object to apathy," "hypokinesia" and "insensitiv[ity] to quite gross visual

stimuli." 62 Electrical stimulation at frequencies above 20 Hz. of single loci in the cat putamen causes cortical EEG desynchronization, opening of the eyelids and dilatation of the pupils.; However, stimulation of those same loci at frequencies below 9 Hz. causes cortical EEG synchronization, "closing of the eyelids accompanied by a narrowing of the pupils." 61 Repeated or longÐterm low frequency stimulation of the putamen causes motor inhibition where all spontaneous activity stops and the animal remains motionless. "In this sleepÐlike state the eyes will be closed or halfÐclosed, even when the animal is not lying down." 61

These findings suggest that the integrity of putamenal neurons and the rate at which corticostriatal efferents stimulate them regulate the state of activation of the animal in terms of its ability to direct attention, perform motor behavior and even maintain wakefulness. 73,74

Pallidum as Phasic Moderator of Activation. The putamen's regulation of cortical and motor activation is accomplished directly through its inputs to the pallidum. Two types of putamenal medium spiny neurons (MSN) receive cortical efferents and project to the pallidum: Neurons expressing dopamine 1 (D1) receptors on their distal dendritic spines project to and inhibit the firing of the internal globus pallidus (GPi), while neurons expressing dopamine 2 (D2) receptors on their distal dendritic spines project to and inhibit the firing of the external globus pallidus (GPe). 61,64

Putamenal neurons projecting to the GPi are also thought to send inhibitory collaterals to the proximal dendritic shafts of putamenal GPe inhibitory neurons. 65,75 The lateral inhibition of GPe inhibitory neurons by MSN that inhibit the GPi is the simplest explanation for electrical stimulation of the putamen (but not the GPi) producing cortical and behavioral activation identical to that achieved by direct stimulation of GPe. 61

Putamenal inhibition of the pallidum has two opposite effects. Inhibition of the GPi reduces the firing of its GABAergic efferents which tonically inhibit the ventral lateral and ventral anterior thalamic nuclei. 61-76 When disinhibited, these thalamic nuclei allow cortical desynchronization and send an "enabling" signal to the supplementary motor and premotor motor areas, allowing the initiation of intentional movement and the execution of "learned motor plans." 61-64,77-79

Putamenal inhibition of the GPe reduces the tonic firing of its efferents which disinhibits the subthalamic nucleus (STN), allowing the STN to stimulate the GPi to inhibit the thalamus. Reduced GPe firing also decreases stimulation of the descending reticular formation (dRF) and reduces muscle tone. 61,65,67 The profound consequence of reduced GPe firing is seen in the akinetic mutism resulting from GPe lesions. 62

Substantia Nigra as Tonic Moderator of Activation. The release of dopamine from the substantia nigra pars

compacta (SNc) increases the level of excitability of putamenal GPi inhibitory neurons via stimulation of D1 receptors, and inhibits putamenal GPe inhibitory neurons via D2 receptor stimulation. 64,65 The SNc also sends excitatory inputs to the dRF that enhance muscle tone. 61 Decreased dopaminergic input to the putamen in humans decreases the diffuse activation of the cortex and the ability to Òmaintain targeted attentionÓ and even produces akinesia - symptoms that can be reversed to some extent by the administration of L-Dopa or dopamine receptor agonists. 81,82 A reduction in dopaminergic input to the lenticular nucleus in Parkinson's disease (PD) has been implicated as the cause of hypokinesia, bradykinesia, and the impaired ability to "transfer attention." 81,82

It is noteworthy that fatigue itself is also a prominent (albeit infrequently described) symptom of PD. 83 "Excessive fatigue" was reported by 48% of PD patients in one study, while nearly one-third of PD patients reported that fatigue was their "most disabling symptom." 83,84 One of the first descriptions of cognitive dysfunction in PD could serve as a definition of post-viral fatigue, i.e., a syndrome Òcharacterized by a diminution of voluntary attention, spontaneous interest, initiative and the capacity for effort and work, with significant and objective fatiguability, and a slight diminution of memory.Ó 85

Physiology of NonÐPathological Fatigue. Fatigue may occur normally when a reduction in the activation of the cortex

decreases the firing of cortical efferents to the putamen. (Fig. 3) The resulting decrease in putamen MSN firing would decrease inhibition of the GPi, permit continued inhibition of the GPe and decrease stimulation of the dRF, allowing a reduction in muscle tone and reduced aRF stimulation of the cortex. Inhibition of the GPe would disinhibit the STN, allowing it to stimulate the GPi to inhibit thalamic nuclei, prevent release of the motor activating set, halt execution of learned motor plans, stop intentional movements, increase cortical synchronization and promote sleep in animals who have no conscious awareness of fatigue. Humans would subjectively perceive these events as the "aversion to effort,Ó feelings of passivity and difficulty staying awake that are symptoms of fatigue. 86 Inhibition of the motor activating set and decreased dRF activity could also generate two of the peripheral signs of central fatigue - the relaxation and lack of recruitment of motor units - that may underlie the visceral feeling of ÒexhaustionÓ that accompanies fatigue. 86 In both humans and animals, rest or sleep would restore cortical activation and stimulation of the putamen, which would inhibit the GPi, disinhibit the GPe, release the motor activating set, and restore activity within the reticular formation to reinforce cortical activation, release learned motor behavior and allow intentional movement.

Pathophysiology of PostÐPolio Fatigue. Polio survivors' chronic fatigue, or the excessive fatigue that follows mild activity or emotional stress, may result from poliovirus lesions in brain biasing the BFG in favor of the fatigue

generating process described above. A reduction cortical activation may result from poliovirus damage to neurons in the motor and premotor areas decreasing the firing of cortical efferents to the putamen. (Fig 4). Poliovirus lesions in the putamen, globus pallidus, thalamus and midbrain reticular formation may also: 1) reduce putamenal inhibition of the GPi and prevent disinhibition of the GPe (allowing chronic STN stimulation of the GPi); 2) prevent thalamic nuclei from stimulating motor and prefrontal cortices; and 3) decrease stimulation of the dRF, reduce muscle tone and thereby decrease muscle spindle efferent activation of the aRF and the cortex.

These impairments of phasic activation of the brain may be superimposed on impairment of tonic activation of the putamen and dRF resulting from poliovirus lesion in the substantia nigra. A decrease in dopaminergic input could bias the putamen in favor of disinhibiting the GPi (as a result of decreased stimulation of excitatory D1 receptors on GPi inhibitory neurons) and maintaining inhibition of the GPe (as a result of decreased stimulation of inhibitory D2 receptors on GPe inhibitory neurons). Decreased SNc output would also reduce dRF stimulation, decrease muscle tone and aRF activity, as well as reduce direct dopaminergic stimulation of the cortex. 87 SPECT scans in patients with ME showing significantly decreased perfusion of the brain stem have provided the first evidence that a decrease in the activity of brain stem (possibly reticular formation) neurons is associated with chronic fatigue. 88

These putative effects of poliovirus lesions in the motor cortex, basal ganglia, thalamus, and reticular formation may be reinforced by poliovirusÐlesions in other areas of the CNS. White matter hyperintensities on MRI in polio survivors reporting fatigue may be evidence of damage to myelinated fibers, or their wallerian degeneration due to gray matter lesions, which may compromise transmission between or partially disconnect the thalamus and the cortex. 52,89,90 The decreased secretion of ACTH in polio survivors with fatigue, possibly resulting from poliovirus lesions within the paraventricular nucleus of the hypothalamus (PVN) or pallidal neurons projecting to the PVN, may also contribute to a generalized impairment of brain activation. 17,91 Polio survivors, regardless of their level of fatigue, have been shown in two separate studies to have an impairment of visual memory, a function ascribed to the right hemisphere (RH). 40 Since the RH is thought to play a central role in both cortical activation and preparation for movement, and right hemisphere lesions are associated with reduced cortical and behavioral activation, hypokinesia and even akinesia, polio survivors may have a hemispheric predisposition to decreased cortical activation and fatigue. 40,92,93 Finally, ubiquitous damage to anterior horn motor neurons may tonically reduce muscle tone, muscle spindle afferent stimulation of the aRF, predisposing polio survivors to decreased cortical activation and fatigue. 12

TREATMENT OF POST-POLIO FATIGUE WITH A DOPAMINE RECEPTOR AGONIST

The central role of the basal ganglia in the putative Brain Fatigue Generator suggests that stimulation of its dopaminergic efferents might increase cortical activation, counter attentional impairments, release the motor activating set and reduce the symptoms of fatigue. Therefore, bromocriptine mesylate (Parlodel ¨ ; Sandoz), a directÐacting, postÐsynaptic dopamine 2 (D2) receptor agonist, was chosen for a placeboÐcontrolled pilot study of a pharmacological treatment for postÐpolio fatigue.

Eighty-three polio survivors (who were without comorbidities that could cause fatigue or cognitive problems) completed treatment with the Kessler PostÐPolio Service and complied with conservative therapies for fatigue (energy conservation, work simplification, pacing, daily rest periods.) Regardless of the severity of their fatigue before treatment, only 10 (12%) reported a typical daily fatigue level greater than moderate (the inclusion criterion for the study) after treatment. Two patients were diagnosed as having a major depressive episode and five of the remaining patients agreed to participate in the drug study. Four of those subjects rated their usual daily fatigue as severe and were on Social Security disability as a result of fatigue preventing continued employment. The remaining subject rated her daily fatigue as moderate but was only able to work partÐtime.

Subjects were given log forms and instructed to rate their fatigue upon awakening, at 12:00, 3:00, 6:00 and 9:00 PM.

At 9:00 PM, subjects were instructed to describe any side effects experienced during the day and rate their overall difficulty with motivation, attention, mind wandering, thinking clearly, concentration, word finding, object naming, memory, staying awake during the day, and muscle weakness.

Subjects were given placebo for 28 days and then increasing doses of bromocriptine for 28 days up to a maximum of 12.75 mg/day. Three subjects reported a noticeable reduction in fatigue and related cognitive symptoms on bromocriptine as compared to placebo. These drug responders reported that they "felt awake" and "had a clear head" for the first time in many years; their daily symptoms logs documented decreased difficulty with attention and other cognitive symptoms, motivation and morning fatigue that were significantly correlated with days on bromocriptine, but not with days on placebo (Fig.5). Drug responders' fatigue decreased to below "moderate" at the highest dose of bromocriptine, with fatigue upon awakening decreasing 55%.

Drug responders had more severe CNS abnormalities at baseline than did non-responders; they had more than twice as many hyperintensities on MRI of the brain, a mean plasma ACTH that did not increase following an overnight fast, and clinically abnormal scores on neuropsychological tests of attention (Trail Making Test (Part A)), information processing speed (Paced Auditory Serial Addition Test (2.4

numbers/second presentation speed)), distractibility and vigilance (Gordon Diagnostic System). 94 A resting mean prolactin level nearly double that of the non-responders suggested chronically reduced dopaminergic inhibition of prolactin secretion in the drug responders.

These preliminary findings support the BFG model that suggests inhibition of putamenal MSN that inhibit the GPe, via stimulation of their D2 receptors, may reduce symptoms of fatigue. This conclusion is also supported by a placebo-controlled study of healthy subjects who were administered remoxipride, a potent and selective D2 receptor antagonist. 95 The most frequently reported effects of D2 blockade were "moderate fatigue," "mild somnolence" and "difficulty concentrating." Statistically significant, dose-related increases in subjective "drowsiness" and scores on neuropsychological tests of auditory vigilance, continuous attention and critical flicker fusion were also found following D2 blockade.

We are continuing to test the Brain Fatigue Generator model by measuring attention, EEG power spectra, and plasma prolactin in polio survivors reporting chronic fatigue. We are just beginning studies of patients with CFS using this same protocol to determine if the BFG model is applicable to the pathophysiology of CFS.

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FIGURE LEGENDS

Figure 1. Brain areas lesioned by the polio virus as seen in 158 human autopsies. Severe lesions: Reticular formation (RF); vestibular nuclei (V); cerebellar roof nuclei (R); periaquiductal gray (PG). Moderate lesions: Paraventricular hypothalamic nucleus (PV); posterior hypothalamic nuclei (P); substantia nigra (SN). Mild lesions: Globus pallidus and putamen (GP); locus ceruleus (LC); median raphe nuclei (MR); preoptic hypothalamic nuclei (PO); thalamic nuclei (T).

Figure 2. A putative model of the brain fatigue generator. In the awake and moving animal, cortical activation would stimulate firing of putamen neurons. Putamenal efferent activity would inhibit the internal globus pallidus (GPi), decrease inhibition of the external globus pallidus (GPe), and maintain inhibition of the subthalamic nucleus (STN) to prevent its stimulation of the GPi. Lack of GPi inhibition of the ventral lateral (VL) and ventral anterior (VA) thalamus would allow activation of the frontal cortex (promoting wakefulness and allowing directed attention), release the

motor activating set (allowing intentional movement), stimulate the descending reticular formation (dRF) (to increase tonic motor unit activity and muscle tone), and increase ascending reticular formation (aRF) inhibition of the reticular thalamic nucleus (RTN), thereby allowing a further increase in thalamic activity and cortical activation. (Solid lines: Excitatory neurons; Stippled lines: Inhibitory neurons. Width of lines indicates level of neuronal activity). SNc: Substantia nigra pars compacta; D1: Dopamine 1 receptors; D2: Dopamine 2 receptors. (Reciprocal connections between SNc, cortex, thalamus and putamen omitted for the sake of clarity.))

Figure 3. The brain fatigue generator in non-pathological fatigue. Normally, symptoms of fatigue would result from a reduction in cortical activation that would reduce the firing of putamen neurons. A decrease in putamenal efferent activity would disinhibit the GPi, maintain inhibition of the GPe, and allow disinhibition of the STN stimulation of the GPi. The GPi would inhibit VL and VA thalamic stimulation of the cortex (impairing directed attention and wakefulness), inhibit release of the motor activating set (producing "aversion to effort"), reduce stimulation of the dRF, decrease tonic motor unit activity and muscle tone (producing feelings of "exhaustion"), and decrease aRF disinhibition of the RTN, thereby allowing a further reduction in cortical activation.

Figure 4. The brain fatigue generator after poliovirus

infection. Poliovirus lesions (*) would impair phasic activation of the putamen, GPe, reticular formation, thalamus, motor cortices and their myelinated connections. Lesions in the SNc would reduce dopaminergic stimulation of the putamen and bias the tonic activity of the lenticular nucleus in favor of GPi excitation and GPe inhibition, thereby inhibiting the thalamus, cortex and reticular formation, and producing symptoms of chronic fatigue. Figure 5. Daily logged fatigue and symptom difficulty levels in the drug responders on placebo and at the highest dose of bromocriptine.

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