Quantitative Electroencephalographic Assessment of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Support for a Novel Diagnostic Protocol

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Abstract

The historical infectious disease Myalgic encephalomyelitis (ME) also erroneously known as chronic fatigue Syndrome (CFS) termed "ME/CFS" represents a complex area of difficulty for the modern medical profession where it is commonly held that no empirical diagnostic tests exist to solve its mystery. Confusion surrounding ME/CFS has frequently led to unfounded psychiatric interpretations and application of associated treatments including graded exercise therapy (GET) which is harmful to patients (Twisk & Maes, 2009). The Nightingale Research Foundation (NRF) led by Dr. Byron Hyde have developed an empirically testable and non-falsifiable ME/CFS criteria defined by a) SPECT (Single Positron Emission Computed Tomography) demonstrating diffuse vascular hypoperfusion over key areas of cerebral cortex and b) persisting enteroviral presence in the gut measured with immunoperoxidase staining (Hyde, 2017, Chia et al, 2009). NRF's data strongly support that both poliomyelitis and ME/CFS represent enteroviral central nervous system pathologies secondary to insufficient blood supply caused by vascular cuffing. The present study was conducted to independently assess NRF SPECT findings using qEEG (Quantitative Electroencephalography) coupled with sLORETA (Standardized Low-Resolution Electromagnetic Tomography) software. Forty-five adult volunteers (aged 18 or over) with a medical diagnosis of ME/CFS were recruited. An aggregate brain representing 675 minutes of eyes-closed data was assembled from the group and compared to the sLORETA BRL normative database in the frequency range between 1.5-35Hz. Results show 13 source localizations significant ($z= 3.085$, $p= 0.001$) overlap with key NRF SPECT findings. NRF SPECT findings can be independently confirmed with qEEG coupled with sLORETA and neuroanatomically support signs and symptoms of the disease first documented in 1934. SPECT and qEEG should

be immediately taken up by the scientific and medical professions as definitive standards for measuring ME/CFS.

Acknowledgements

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Dr. Byron Hyde M.D. of the Nightingale Research Foundation has generously provided permission for the use of images from their publications to be included herein and additional support via personal correspondence allowing this document to benefit from his unparalleled expertise in this field; both are acknowledged with gratitude and appreciation.

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Finally, the author wishes to acknowledge with warm appreciation each of the 45 volunteers themselves. Not only did they supply the raw data required to measure this unique illness but welcomed us into their homes and shared their remarkable life stories.

Introduction

Myalgic Encephalomyelitis, also erroneously known as Chronic Fatigue Syndrome (CFS) primarily in the USA is an acute onset enteroviral encephalopathy. Correct definition requires **1)** acute onset and often biphasic (i.e. including a prodrome before the chronic phase) disease as in poliomyelitis **2)** occurring primarily from June to November in the northern temperate climate, **3)** recovery of evidence of enteroviral infection either directly or by association with others with enteroviral disease including **but not limited to** enteroviral pneumonia, hand foot and mouth disease, and herpangina (severely painful blistering of the buccal area caused by Coxsackie or echoviruses), **4)** occurring as an epidemic or sporadically, **5)** evidence of anterior temporal lobe and posterior cingulate hypoperfusion injury best seen on Segami Oasis HMPAO SPECT brain imaging software **6) Symptoms:** Approximately 50% of the symptoms directed to significantly abnormal CNS function, including memory and motor cortex difficulties and complaints: all ME patients have both memory and motor dysfunction. **7)** as in acute poliomyelitis most patients recover or are not significantly injured by these enteroviruses; only the chronic, more severe condition in either poliomyelitis or ME are known by their disease name – prior to the Salk and Sabin immunizations polio and ME occurred simultaneously during the same epidemics (B.M Hyde, personal communication, April 4, 2019).

The definition of CFS was developed in 1988 (Holmes et al, 1988), and in 1994 (Fukuda et al, 1994) by the USA CDC Atlanta and the NIH in Maryland. It was based upon the misconception in 1988 that the syndrome was caused by Epstein Barr virus (EBV). This EBV belief was dropped from the 1994 definition but only after they were informed that EBV has an incubation period usually between 25-50 days and therefore could not be a rapidly spreading infectious disease. Both CFS definitions were almost entirely based upon symptoms common to many separate and diverse

pathological conditions. Some of these pathologies are progressive and can lead to death as in missed malignancies often with the same symptoms, various missed cardiac conditions and a wide variety of CNS injuries including diverse viral infections, toxic chemical injuries, traumatic incidents and a variety of missed genetic abnormalities (B.M. Hyde, personal communication, April 4, 2019).

ME follows similar patterns to poliomyelitis, Acute Flacid Paralysis/Acute Flacid Myelitis, each of which follow one or more enteroviral infections (B.M. Hyde, personal communication, April 4, 2019).

Enormous confusion has accumulated around ME/CFS, with the medical profession often interpreting it as psychiatric and amenable to associated therapies despite repeated failure while a plethora of other inquiries have pursued hypotheses from Epstein Barr virus, XMRV virus, mitochondrial dysfunction, neurally mediated hypotension, and myriad others (Surawy, et al, 1995, Holmes et al, 1988, Erlwein et al, 2010, Booth et al, 2012, Rowe et al, 1995).

Despite these efforts, the ME/CFS problem has remained firmly entrenched even grown more prominent with the rise of the internet. This has facilitated assembly of support groups, bringing affected persons from around the world together in hopes of developing more effective self-advocacy (https://www.millionsmissingcanada.ca/, https://mefmaction.com/, https://www.hfme.org/).

ME/CFS has grown into a unique anomaly with supposedly no clear pathology much less treatment and a significant, but poorly defined number of people around the world claiming a serious illness continues to devastate their lives. Substantial difficulty exists in determining the actual prevalence of ME/CFS owing to the myriad definitions available, many of which are indistinguishable from

other, especially psychiatric disease definitions (Reyes et al, 2003, Bates et al, 1993, Costa et al, 1995). Owing to this, a review of the historical literature assembled from the early scientists who first encountered this unique illness is necessary, followed by a description of events in the 1980's most directly responsible for the current state of confusion.

Early History of ME/CFS

The first epidemic of the disease that would come to be known as ME/CFS occurred in Los Angeles California during the summer of 1934 concurrently with an epidemic of poliomyelitis (Gilliam, 1938). While diagnosed unsatisfactorily at the time as poliomyelitis the epidemiological and clinical features could not entirely be reconciled in as much as 1) all 198 cases were *adult* employees of the Los Angeles County Hospital 2) the definitive paralysis accompanying poliomyelitis was strikingly absent, and 3) an unusually high proportion of females younger than 30 years old were affected (Gilliam, 1938). The epidemiology of this first unusual "polio-like" epidemic was extraordinary for the time, held as potentially representing the first manifestation of a new polio form, or something else entirely (Gilliam, 1938). The association with polio would turn out to be an essential clue to the mystery.

Poliomyelitis, also known as infantile paralysis was widely known as a terrifying infectious disease affecting children, appearing annually during the summer months producing a characteristic febrile illness that too frequently lead to paralysis or death secondary to injury of structures in the brain and especially spinal cord (Fischer & Stillerman, 1937). Individuals of any age could potentially be infected with polio and variously recover completely, partially, or not at all, demonstrating considerable variability known to depend on factors including host response, measures of

communicability or virulence and the pre-existing medical conditions of those encountering the virus (Fischer & Stillerman 1937).

Early stage ME/CFS symptomatology following a 3-6-day incubation period included nausea, vomiting and diarrhea which are still considered typical of the nonspecific febrile illness associated with enteroviral infections including the annual flu (Gilliam 1938, Zaoutis & Klein, 1998). Symptomatology through the first week diverges from poliomyelitis, and commonly includes highly variable somatic pain, unusually severe crushing headaches over variable cranial regions, muscle tenderness, somatic sensory disturbances i.e. tingling or "pins and needles sensation", stiffness of the neck and back resembling meningitis, severe constipation, and paresis of variable muscles or muscle groups often including fasciculations (Gilliam, 1938).

Vertigo, visual disturbances including photophobia, extreme irritability and an array of other features were documented among the group, but the precise symptomology was highly variable with no one person exhibiting all features (Gilliam, 1938). Unusually still, impairments with memory, concentration and sleep disturbances were recorded, along with the unique phenomenon that symptoms became worse upon even minor cognitive or physical exertion. This easy deterioration both cognitively and in musculature went on to generate substantial difficulties in returning to previous work life (Gilliam, 1938). In following up on this first group years later it was discovered that none fully recovered, having lived out their lives in the chronic disease state now considered typical of ME/CFS with profound cognitive and physical limitations (Hyde, 2017).

Through the 1930's subsequent epidemics are documented in Switzerland. The first appearing during the summer of 1937, affected 130 soldiers at a military hospital in Erstweld, and the second

that same autumn at St. Galls Hospital women's ward, reiterating the same illness documented by Gilliam (Parish, 1978). This is repeated once more in Degersheim Switzerland in 1939, concurrently with a poliomyelitis epidemic affecting some 73 individuals (Parish, 1978).

Between 1948 and 1949 Iceland saw the largest documented epidemic, affecting some 1080 people, with the town of Akureyri accounting for some 465 individuals (Sigurdsson et al, 1950, Henderson & Shelokov, 1959, Hyde, 1992). Epidemiologically the illness continued to preferentially affect adult females with the highest instance in 15-19-year-olds. Again, the illness was characterized by a highly protean symptomatology commonly including somatic pain, paresthesia, variable muscular paresis, severe constipation, irritability, sleep disturbances, impaired memory, dizziness and others (Sigurdsson et al, 1950). The characteristic deterioration in response to even minor exertion is again confirmed to exacerbate symptoms or induce new ones (Sigurdsson et al, 1950).

In 1956 "Benign Myalgic Encephalomyelitis" was proposed as a name and seems to have fared best at representing the illness (Lancet, 1956). This is a combination of the root words myalgia: muscle pain and encephalomyelitis: inflammation of the brain and spine, representing the pathology implied by the symptoms. The disease had been previously called variously "disease simulating poliomyelitis", "abortive poliomyelitis", "epidemic neuromyasthenia", "Akureyri disease" among many others according to the disparate scientists documenting it. The book "Disease of a Thousand Names" summarizes the plethora of names associated with the illness (Bell, 1991).

Even at first glance the symptomatology suggests that like poliomyelitis, a definitive central nervous system pathology is an inescapable conclusion. Based on the paresis, unusual headaches, somatic sensory disturbances, emotional lability and memory loss however one might easily

suspect the brain itself, as opposed to the spine to be the primary site of injury (Forster, 1973, Weiner & Levitt, 1989). Supporting evidence for this is perhaps first and foremost given by the prominence of the "severe crushing headache" documented among the most common symptoms (Gilliam, 1938). This is extremely notable in that reports of unusually severe headache are in modern times considered significant clinical indicators of subarachnoid hemorrhage, stroke, or meningitis, all phenomena directly related to the brain's vasculature (Morgenstern et al, 1998, Vestergaard et al, 1993, Rotbart et al, 1998).

Prophetically, in documenting the effects of transferring toxic metabolites found in the urine of patients unique in a 1955 epidemic to monkeys Parish discovered formation of "disseminated lesions scattered throughout the nervous system from the brain to peripheral nerves and associated with perivascular round cell infiltration without significant cellular damage" (Parish, 1978).

Modern History of ME/CFS

By 1992 a record was constructed of 63 epidemics around the world with the largest being 1948-49 northern Iceland, affecting 1090 people, Adelaide Australia 1949-1951 affecting 800 people, and 1954 Tallahassee Florida affecting 450 people (Hyde et al, 1992). Among these are many smaller clusters including as few as 7 people and does not include sporadic individual cases which have historically been much more prone to being overlooked (Keighley & Bell, 1983). From this a picture can be constructed showing that all large epidemics occur prior to the original Salk polio vaccine. By the time polio has been significantly reduced in the 1960's what remains of ME/CFS are smaller clusters and sporadic cases, strongly suggesting the vaccine affected an underlying enteroviral pathology as seen in Figure 1 below (Caceres & Sutter 2001, Hyde et al, 1992, Hyde 2017).

This is supported by the fact that the group of enteroviruses differ from each other by only 5% of their total genome and are especially capable of recombination wherein genomic material is hybridized between one or more viruses creating myriad variations on top of an already high mutation rate due to their property of low fidelity replication (Hyde, 2017, Li et al, 2005). Exemplifying this special property, it is well known that many separate enteroviruses may all produce hand foot and mouth disease which, like historic poliomyelitis is modernly most common in children (Li et al, 2005). Lesser known or perhaps forgotten modernly, the coxsackie, echo and other enteroviruses are also known to be capable of producing poliomyelitis (Malzberg et al, 1993). Given that ME/CFS was always an outlier related to polio, combined with the disappearance of its large epidemics, the perception of a serious public health threat seems to have been even more greatly reduced by disappearance of polio. This has led to a seemingly ill-conceived confidence in dismissing continued research into enteroviral pathology as an essential to public health (Hyde, 2017).

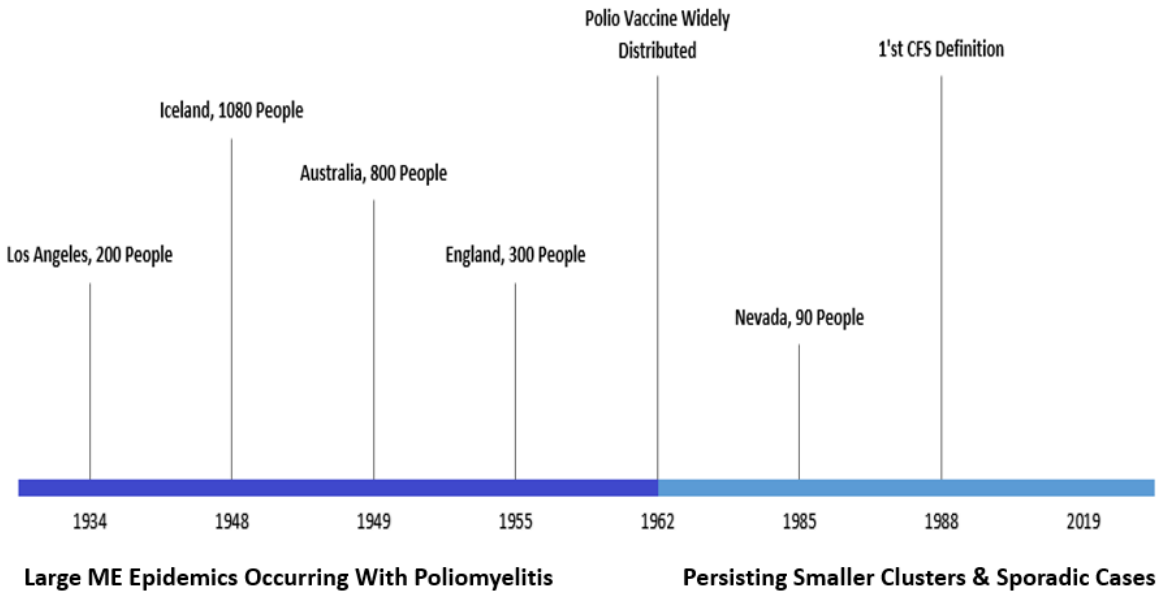

Figure 1. Large ME/CFS epidemics from the earlier part of the last century disappear following introduction of the polio vaccine.

Chronic Fatigue Syndrome

By 1985 another smaller cluster of some 100 people appearing in Nevada leads to the first definition of "Chronic Fatigue Syndrome" (CFS) which summarily dismisses the wealth of historical information relating enteroviruses to ME and creates a new disease definition defined solely as *untestable* fatigue on the meager basis that the incubation period of Epstein-Barr virus is too long to be at fault (Holmes et al, 1987, Holmes et al, 1988). Fatigue is part and parcel of a wide variety of normal experience plus an enormous array of different illnesses; the phenomenon itself has no empirical measurement and therefore no ability to differentiate among supposed types (B.M Hyde, personal communication, April 4, 2019). This unfounded summary dismissal of infectious agents and uniquely aberrant disease definition seem to have set the modern medical community into an increasingly irrational tailspin where self-defeating "chronic fatigue" definitions begin to replicate. These include the 1991 "Oxford" definition, and 1994 "Fukuda" criteria (Sharpe, 1991, Fukuda et al, 1994).

Concerning CFS definitions, interest is in solely the subjective phenomenon of unusual fatigue, going so far as to exclude a CFS diagnosis if *any* measurable pathology is discovered. Presence of a psychiatric disorder such as depression is likewise *not* considered grounds for exclusion, thereby conceptually establishing all CFS as psychiatric disorders and presumably amenable to psychiatric treatments (Sharpe et al, 1991, Fukuda et al, 1994). Unquestioned confidence that a discrete pathological entity implied by CFS criteria could exist at all coupled with ignorance of the historical medical outlier ME, essentially an obscure footnote in the presumably solved problem of polio has been an enormous advantage for the illness originally described by Gilliam (Hyde, 2017).

The foisting of the CFS construct onto ME, now termed ME/CFS has led to profound, often bitter acrimony between patients and the medical, especially psychiatric community where conventional treatment is still often graded exercise therapy (GET), despite decades of patients insisting the procedure is at best useless and frequently is extremely harmful (Twisk & Maes, 2009). By 2011, a spurious study known as the PACE trial was conducted seemingly showing conclusively that combinations of graded exercise therapy (GET) and cognitive behavioral therapy (CBT) were effective for treating ME/CFS and could even be curative (White et al, 2013). This sparked suspicion and substantial criticism from members of the scientific community who found the PACE authors reluctant to provide raw data which was eventually obtained via court order (Vink, 2017). The study was found to be misleading based on a variety of erroneous methodology that according to opponents supports treatment that "creates unnecessary suffering inflicted on patients by physicians" (Vink, 2017).

Emphasizing the persisting confusion created by the aberrant CFS construct after 27 years of failed research, 2015 saw the introduction of SEID (Systematic Exercise Intolerance Disease), yet another CFS replica already lost among the growing morass of definitions (Clayton 2015, Jason et al, 2014, Jason et al, 2015). Authors of the PACE trial have seemingly continued to pursue erroneous research under criticism (Vink, 2017). One wonders where the patient's voices are in all this, but then they do not tend to publish in scientific journals.

Nightingale Definition of ME/CFS

Dr. Byron Hyde and the Nightingale Research Foundation (NRF) have taken an organized scientific approach to understanding ME/CFS in "Clinical and Scientific Basis of ME/CFS" first assembling and analyzing the extensive array of related findings from the first modern encounter

until it's publication in 1992 (Hyde et al, 1992). Images from NRF's publications are reproduced herein with full permission graciously provided (Appendix A).

Most essentially the NRF has developed an empirically testable, non-falsifiable definition of ME/CFS which is currently:

A) Brain SPECT (Single Positron Emission Tomography) scan demonstrating diffuse vascular hypo-perfusion.
B) Gastric biopsy demonstrating an active, persisting enteroviral presence in the gut.

NRF SPECT findings clearly demonstrate the pathogenic effects of exercise on the ME/CFS brain as seen in Figure 2 (Hyde et al, 1992). Presently, NRF SPECT imaging of ME/CFS has become much clearer shown in Figure 3 (Hyde, 2017). Definitive ME/CFS lesion sites on SPECT are the left anterior temporal lobe and posterior cingulate cortices, often including similar findings in the right temporal lobe (Hyde, 2017). Patchy hypoperfusion over additional cortex is variable but often includes the motor and somesthetic cortices (Hyde, 2017).

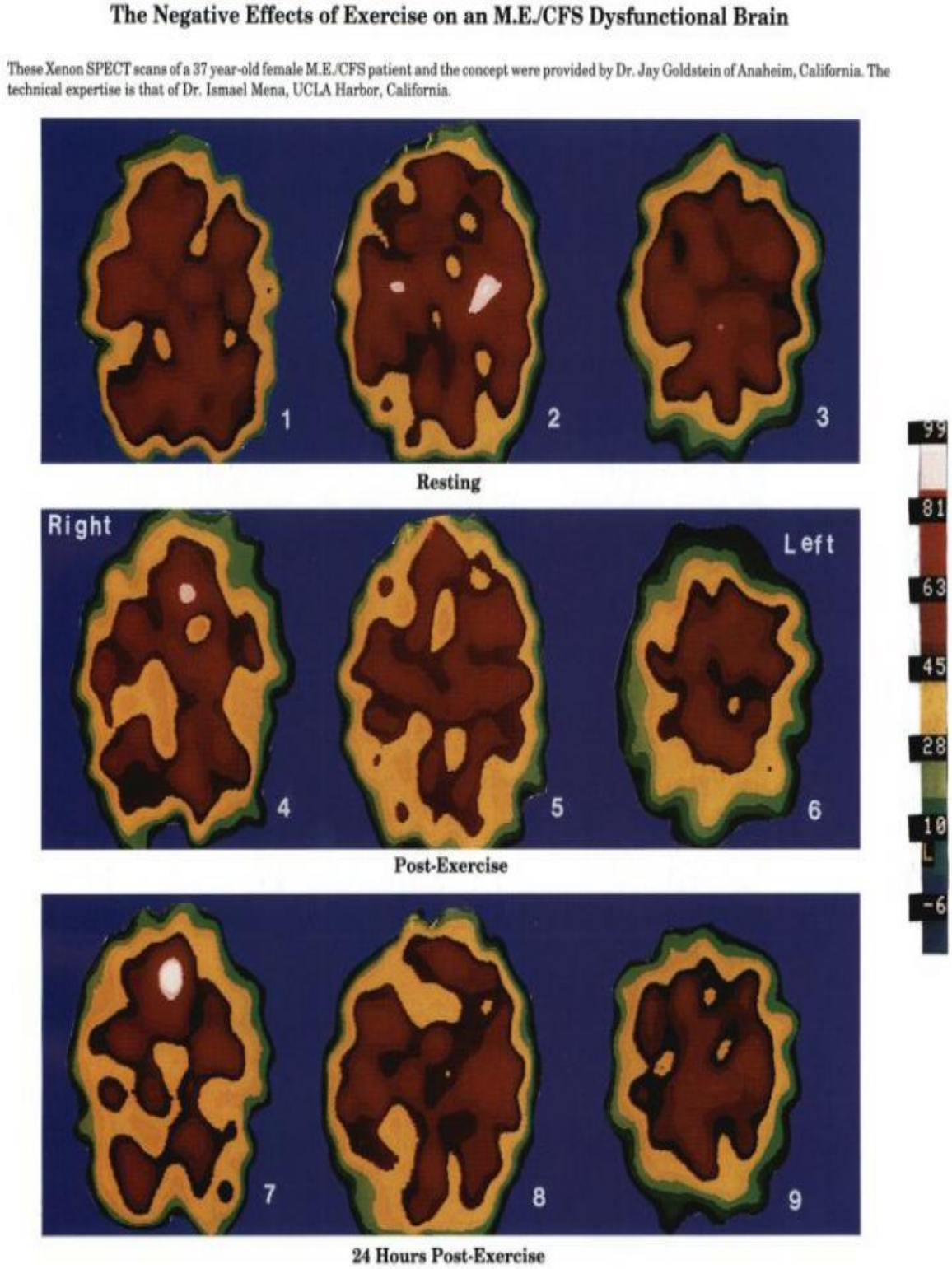

Figure 2. Already low blood supply in the ME/CFS brain are worsened with exercise shown on SPECT; right and left hemispheres are here represented in reverse. (Hyde et al, 1992). Note the hypoperfusions at lateral boundaries represented by green through black on the color scale.

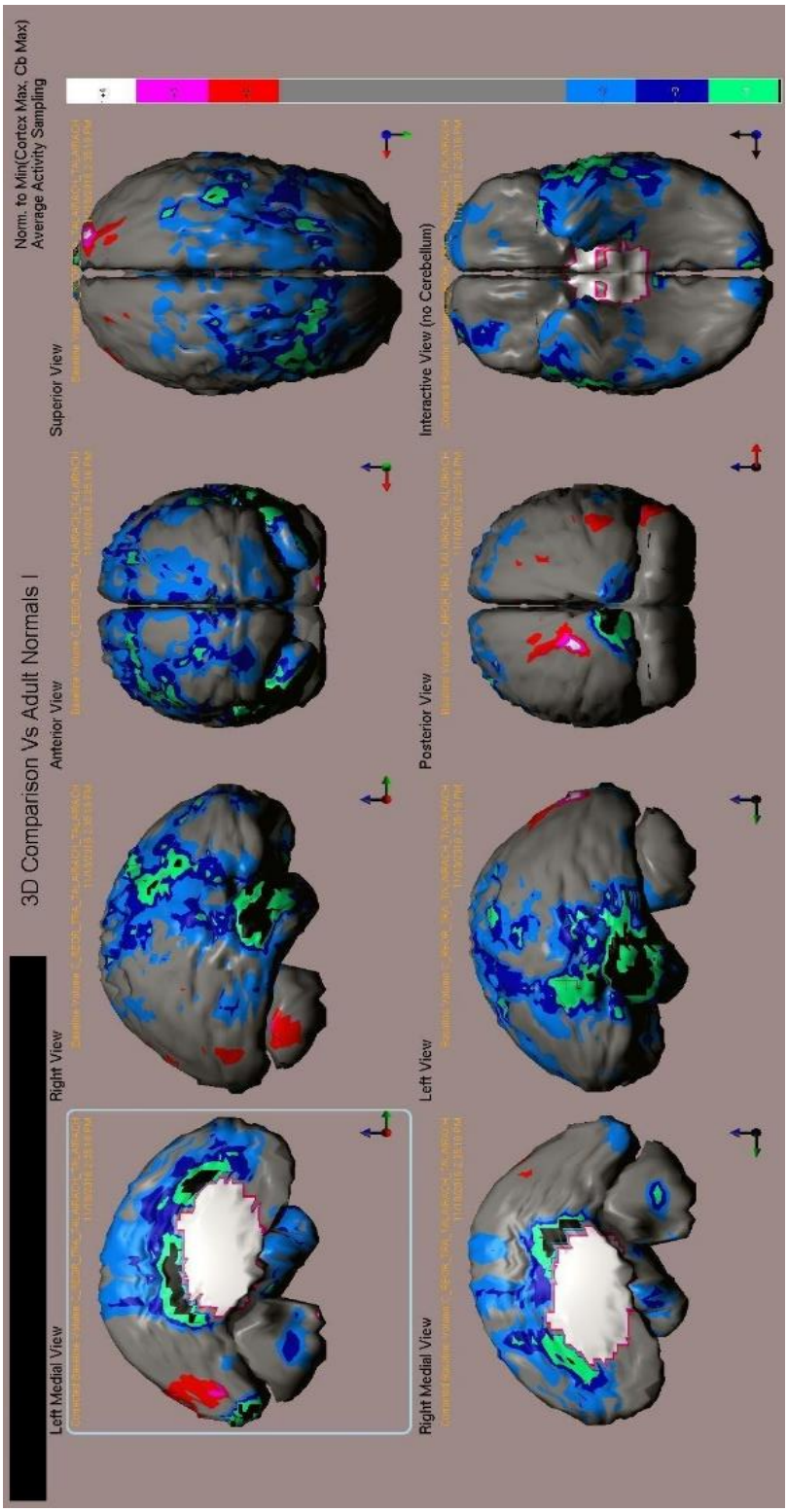

Figure 3. Modern SPECT imaging using cutting edge Segami Oasis software provide much higher resolution, detailing the patchy diffuse vascular hypoperfusion characterizing the ME/CFS brain (Hyde, 2017).

The gastric biopsy testing included in the NRF ME/CFS definition was pioneered by Dr. John Chia and colleagues in longitudinal follow up of previously well individuals who were hospitalized with acute febrile illnesses and went onto develop ME/CFS (Hyde, 2017, Chia et al, 2009). Testing included immuno-peroxidase staining for proteins of the *entire* enterovirus family and is confirmed with viral RNA assay (Chia et al, 2009). One mechanism by which poliomyelitis compromised neurons is vascular cuffing as seen in Figure 4 showing histology taken from the spinal cord of a poliomyelitis cadaver (Hyde, 2017). A capillary is seen in the center and surrounding are immune cells representing vascular cuffing limiting blood from exiting to the spinal neurons (Hyde, 2017). Vascular cuffing is also known in the spinal cords of patients who suffered from polio as long as twenty years after the fact, demonstrating the phenomenon can be chronic in survivors of enteroviral disease (Malzberg et al, 1993). This information suggests it's self as extremely relevant for the modern phenomenon "Post-Polio Syndrome", a disease so like ME but absent the CFS baggage that they might be confused for each other if not for a history of poliomyelitis (Bruno et al, 1998).

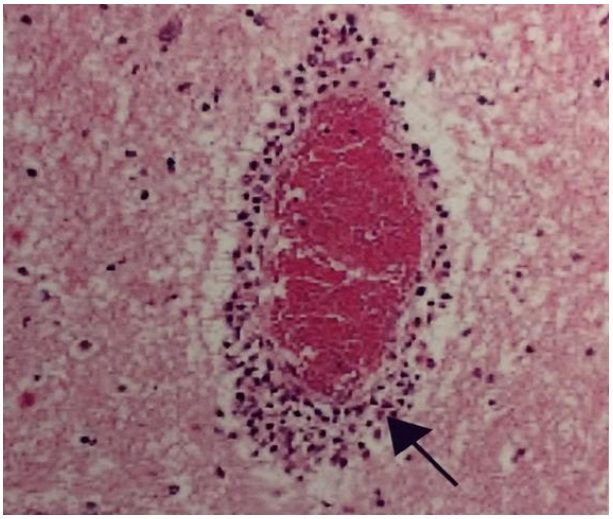

Figure 4. Vascular cuffing impairs blood supply to spinal neurons (Hyde, 2017).

Based on SPECT and gastric biopsy data the ME/CFS disease process fits the same vascular cuffing phenomenon as poliomyelitis with the difference that the polioviruses tend to affect spinal vasculature while the remaining enteroviruses alone or in combination tend to affect the cerebral arteries (Hyde, 2017). This appears sensible given that vaccination has never been developed for the other enteroviruses despite the protean number of diseases they are known to cause including encephalitis, meningitis, pericarditis, myocarditis, hand foot and mouth disease and herpangina all to this day, albeit in relatively small numbers of people (Moore, 1982, Li et al, 2005). From a group of 686 patients admitted to one hospital during the 1935 New York polio epidemic 2% were considered to have encephalitic-polio where the virus was presumably affecting the brain (Fischer & Stillerman, 1937). The NRF points out not only that polio did occasionally enter the brain, but it produced histological findings that when plotted visually overlap exactly with the typical ME/CFS SPECT map (Hyde, 2017).

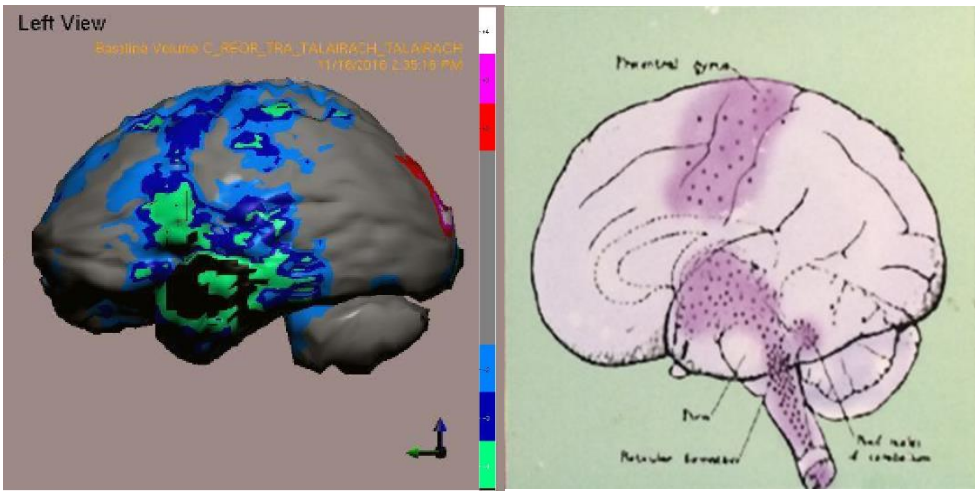

Figure 5. Left: a typical SPECT image of the ME/CFS brain (Hyde, 2017). Right: Histology findings from autopsy of a poliomyelitis brain (Hyde, 2017).

qEEG (quantitative electroencephalography) has previously been shown to be sensitive to vascular-related cerebral changes accompanying stroke as well as neuropsychological functioning (Cuspineda et al, 2003). The present study therefore was intended to obtain independent confirmation of NRF SPECT findings in ME/CFS brains using qEEG (Quantitative Electroencephalography) with sLORETA (Standardized low Resolution Electromagnetic Tompgraphy), a separate functional brain imaging technology.

Materials & Methods

All raw qEEG measurements were made with WINEEG free software version 2.127.98 running on a Windows 10 equipped IBM Thinkpad laptop using a Mitsar model 201 EEG amplifier and Mitsar 10/20 system cap equipped with 19 scalp sensors plus ear reference leads. Normative database comparisons and source localizations were computed using SLORETA free software version 20181107.

Recruitment

Approval to conduct the present study was obtained from the Laurentian Ethics Review Board (Appendix A). 45 individuals age 18 and over with an existing medical diagnosis of ME/CFS in the Toronto and Ottawa areas were recruited to participate in an in-home qEEG investigation of brain functioning. Recruitment was based initially on word of mouth via ME/CFS affected individuals the author was personally familiar with. Efforts were made to reach volunteers with existing SPECT and gastric biopsy results obtained via the NRF. A total of 5 such individuals were recruited who supplied SPECT maps and gastric biopsy results. Their results are reproduced below with permission.

A Canadian charitable organization dedicated to ME/CFS, Millions Missing Canada subsequently contacted the author expressing interest in posting the recruitment script on their website (Appendix B). Upon contacting the author, potential volunteers were supplied with a) the recruitment script, and b) the consent form (Appendix C). Arrangements were made for an in-home visit including the author and a colleague from the Laurentian Behavioural Neuroscience program to perform a qEEG recording. Signed consent forms were obtained either via email or completed in person at the beginning of in-home visits.

Stringent efforts were made to ensure that volunteers' comfort and privacy were protected during the investigation and in subsequent data storage. Efforts included supplying contact phone numbers for the Principal Investigator, Laurentian Ethics Committee for potential complaints and optional password encryption for communication of all personal information. Duration of visits was limited to no more than 1-1.5 hours in order to minimize disruption of daily routines. Additionally, it was clearly communicated and emphasized that the researchers were sympathetic to ME/CFS and familiar with the existing NRF research described above.

qEEG Procedure

A comfortable, quiet and relatively dark place was selected in the home to perform the qEEG. These conditions are required for the most accurate measurements of brain activity; excessive light, noise or commotion in the environment may all have a direct impact on neural behavior and must be kept to a strict minimum, ideally zero to make an unconfounded assessment (Schomer & Lopes da Silva, 2011).

Participants craniums were measured to select an appropriately sized sensor-cap. Each of the caps 19 sensor wells were filled with hypoallergenic conductive gel applied with a blunt syringe to

establish a clear signal into the amplifier (Schomer & Lopes da Silva, 2011). Participants were then asked to sit quietly in relative stillness for recording and guided through alternating 180 second segments of eyes closed and eyes open with a short breathing task according to the paradigm in Figure 6. Intervals between segments were used for participants to change position if necessary, to maintain comfort. 35 minutes of data in total was recorded and saved to laptop hard disk via WINEEG for each participant. Backups of master recordings were made to an external hard drive immediately after each recording.

1) Eyes Open: 180 seconds	9) 4 Second Breathing: 45 seconds
2) Eyes Closed: 180 seconds	10) Normal Breathing: 60 seconds
3) Eyes Open: 180 seconds	11) 2 Second breathing: 45 seconds
4) Eyes Closed: 180 seconds	12) Normal Breathing: 60 seconds
5) Eyes Open: 180 seconds	13) 1 Second Breathing: 45 seconds
6) Eyes Closed: 180 seconds	14) Normal Breathing: 60 seconds
7) Eyes Open: 180 seconds	15) Eyes Open: 180 seconds
8) Eyes Closed: 180 seconds	16) Eyes Closed: 180 seconds

Figure 6. The experimental paradigm conducted in order from 1-16**.**

Artifact Correction

Each participants' complete raw data record was first visually inspected in WINEEG to establish an initial picture of data quality and overall impression. qEEG is subject to a wide variety of signals not generated by the brain (artifacts) including 60Hz wall outlet signal, electrical activity of muscles representing eye blinks, vertical and horizontal eye movements, jaw clenching, talking, coughing, sneezing, position adjustments and other movements (Schomer & Lopes da Silva, 2011). 60Hz wall outlet was filtered out of the raw recordings using the WINEEG notch-filter set to exclude all frequencies from 45-75Hz. Ubiquitous presence of 60Hz noise means actual brain activity within this range is left a mystery and not conventionally measured (White & Van Cott, 2010).

Artifacts directly related to eye-movement tend to be relatively stereotyped and are therefore among the most easily recognized and removed from recordings (Schomer & Lopes da Silva, 2011). WINEEG contains several artifact correction modalities including built in templates for common artifacts that are identified via correlative similarity. This method was ideal for the present study in that a uniform correction needed to be applied to all participants to maintain homogeneity of data processing. WINEEG templates include option to remove both vertical and horizontal eye movement which accounted for a considerable majority of artifacts encountered.

WINEEG's ability to identify an artifact for correlation depends on its presence in the record to begin with. Hence, the records were variously artifact corrected for either a) vertical and horizontal eye movement, or b) vertical eye movement only, according to the individual recordings. The correlation coefficient, i.e. "similarity threshold" to internal artifact models was set to a default of 0.8 (80%) for vertical and horizontal except in two cases where a value of 0.7 (70%) was required. These two exceptions did not appreciably distort or leave the data contaminated based on visual inspection. After template correction records were inspected again visually and remaining artifacts were noted and cut around.

All clean data segments were then extracted from WINEEG as ascii files in preparation for entry into sLORETA software for normative database comparison and source localization of significant anomalies. A total of 675 minutes of eyes closed raw data was extracted from the 45 participants collectively. All data was collected at a sampling rate of 250Hz. Artifact corrected data from all eyes closed segments of all participants was then assembled into a single aggregate ascii file using Matlab software. The aggregate was resampled using sLORETA utilities to 100Hz and a transformation matrix was entered, representing the sensor array's physical coordinates in sLORETA mathematical space. Finally, the aggregate was transformed into a "cross-spectrum"

file using sLORETA utilities representing a density array of recorded signals in the frequency spectrum from 1.5-35Hz that can be compared to normative database.

Source Localization

sLORETA, or "Standardized Low-Resolution Electromagnetic Tomography" is software that allows source localization in 3D brain space (MNI, or "Montreal Neurologic Institute" coordinates), demonstrating point origins in the cortex and hippocampus of signals recorded over the scalp (Pascual-Marqui, 2002). sLORETA operates on the premise that two neighboring neurons are most likely to be active in synchrony, termed "temporal coherence of spatially adjacent neurons". It is extrapolated that this behavioral property represents a mechanism by which more distributed networks function and can hence be measured (Pascual-Marqui, 2002).

Placement of electrodes over the scalp are represented in sLORETA such that they correspond to specific points within a gridwork of 3D points, or "voxels" within mathematical space. sLORETA's brain map contains 6,239 separate voxels of $5mm^3$ each, geometrically representing all cortical neurons derived from MRI based methods of classifying a given cerebral area as neuron, glia, or ventricular (Pasqual-Marqui, 2002).

Neuronal activity under each sensor includes a variety of similar and dissimilar signals compared with all other sensors. Hence, activity at one voxel is compared to every other individual voxel with millions of t-tests serially comparing two averages for statistically significant differences. This allows for emergence of normal, hypo, or hyper activity localization of frequencies between 1.5-35.0 Hz which are finally z-scored against the sLORETA BRL normative database (Pasqual-Marqui, 2002).

Normative Database Comparison

The 675-minute aggregate Fourier derived cross spectrum file was then compared in sLORETA to its internal database of ~100 individuals with brains representing the normal population. Frequency resolution, i.e. the value in Hz separating intervals of the frequency spectrum between frequency measurements was set to 0.39. Lastly the measured spectrum was confined to 1.5-35Hz based on convention and the boundaries of the measurements used to construct sLORETA's internal normative database (Pasqual-Marqui, 2002). A file containing all significant z-scores for anomalies between 1.5-35Hz is the output, specifying the specific anomalous frequency i.e. 5.5Hz in combination with a visual representation of the anomaly's location both in MNI coordinates and modeled on a moveable, interactive 3D Brain. The units of measure are "absolute power" i.e. μv^2, or area under the curve for each frequency on a graph where y= amplitude of voltage and x= time (Pasqual-Marqui, 2002).

Results

13 significant source localizations were discovered among the aggregate of 45 ME/CFS brains representing 675 minutes of eyes closed data compared to normal controls. Z-score defined source localizations were required to be significant at z= 3.085, p= 0.001, and allowed to include additional cortical area significant at a minimum of z= 2.56, p= 0.01.

Table 1. Significant source localizations grouped anatomically.

Brain Region	Brodmann Area	Frequency	Z-score
Right Anterior Cingulate	Brodmann Area 10	11.64Hz	Z= 3.085
Bilateral Anterior Cingulate	Brodmann Area 32	12.03Hz	Z= 3.085
Bilateral Anterior Cingulate	Brodmann Area 25	33.87Hz	Z= 3.085
Bilateral Anterior Cingulate	Brodmann Area 25	35.04Hz	Z= 3.085
Bilateral Superior Frontal Gyrus	Brodmann Area 10	1.5Hz	Z= 3.085

Bilateral Gyrus Rectus	Brodmann Area 11	31.92Hz	Z= 3.085
Bilateral Uncus	Brodmann Area 36	32.7Hz	Z= 3.085
Right Parahippocampal Gyrus	Brodmann Area 28	31.14Hz	Z= 3.085
Right Parahippocampal Gyrus	Brodmann Area 34	32.31Hz	Z= 3.085
Right Parahippocampal Gyrus	Brodmann Area 28	33.09Hz	Z= 3.085
Right Parahippocampal Gyrus	Brodmann Area 28	33.48Hz	Z= 3.085
Right Parahippocampal Gyrus	Brodmann Area 28	34.26Hz	Z= 3.085
Right Inferior Occipital Gyrus	Brodmann Area 19	34.65Hz	Z= 3.085

Discussion

Like epidemic groups from the early part of the last century, the majority of volunteers were female, 84% with only 16% males (Gilliam, 1938, Sigurdsson et al 1950). The mean and median age for the group were both 48 years, with half being between 38 and 60. The oldest participant was a 75-year-old female and the youngest a 22-year-old female. Participant age distribution is represented in Figure 7.

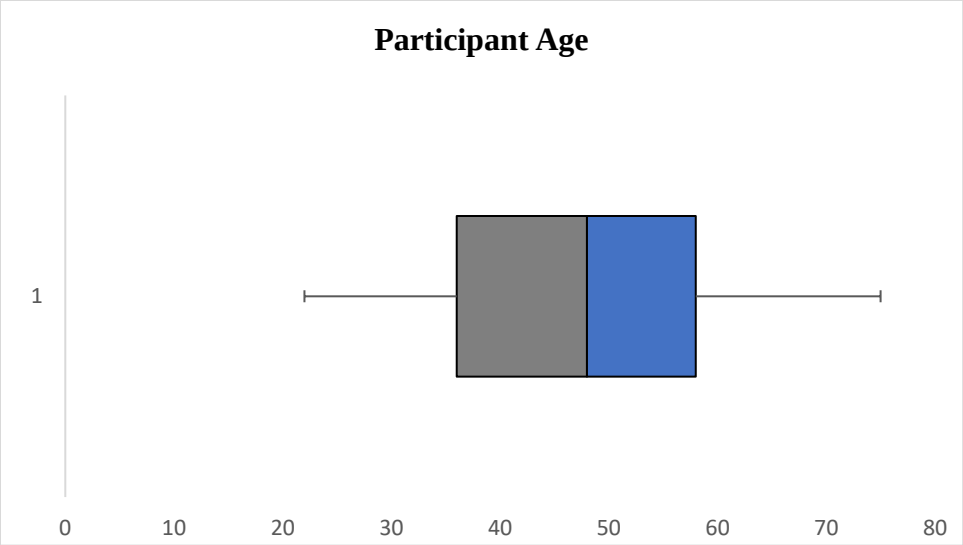

Figure 7. Age distribution of participants.

Comparison with NRF SPECT Data

Color coding of significance for all SLORETA source localizations is according to Figure 8 below with brightest yellow representing z= 3.085 and darkest red representing z= 2.56. NRF SPECT data reproduced with permission (Appendix A) is color coded as seen within images on the right where gray represents normal blood supply, and light blue represents 2 standard deviations (SD's) below normal, dark blue 3, green 4 and black 5. Red corresponds to hyperperfusions 2 SD's above normal, pink to 3 and white to 4. The aggregate of 45 ME/CFS brains is shown on left, compared with NRF SPECT maps of individuals on the right. Historically, structural and functional changes in specific cerebral areas, especially the cerebral cortices have formed the basis of understanding clinical neurologic findings and will therefore be the basis for discussion of findings (Stuss & Levine, 2002).

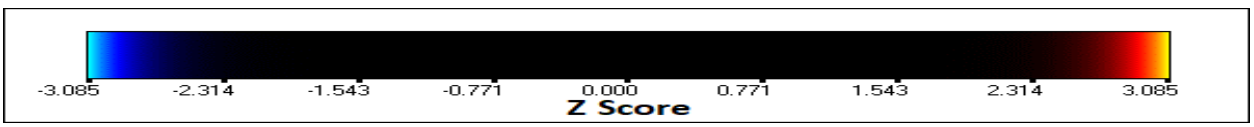

Figure 8. sLORETA color coded z-score scale.

The Left Temporal Lobe

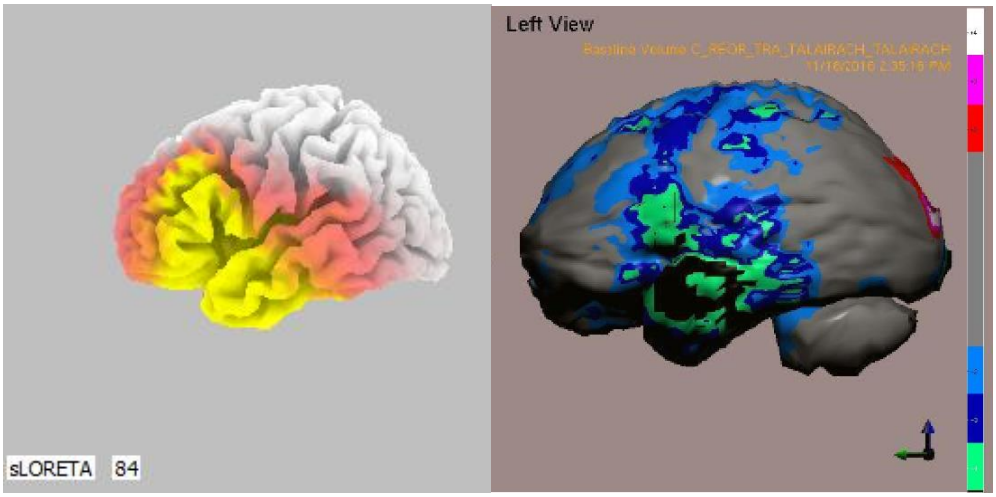

Figure 9. 33.87Hz source localization replicates characteristic NRF ME/CFS SPECT map of diffuse vascular hypoperfusion.

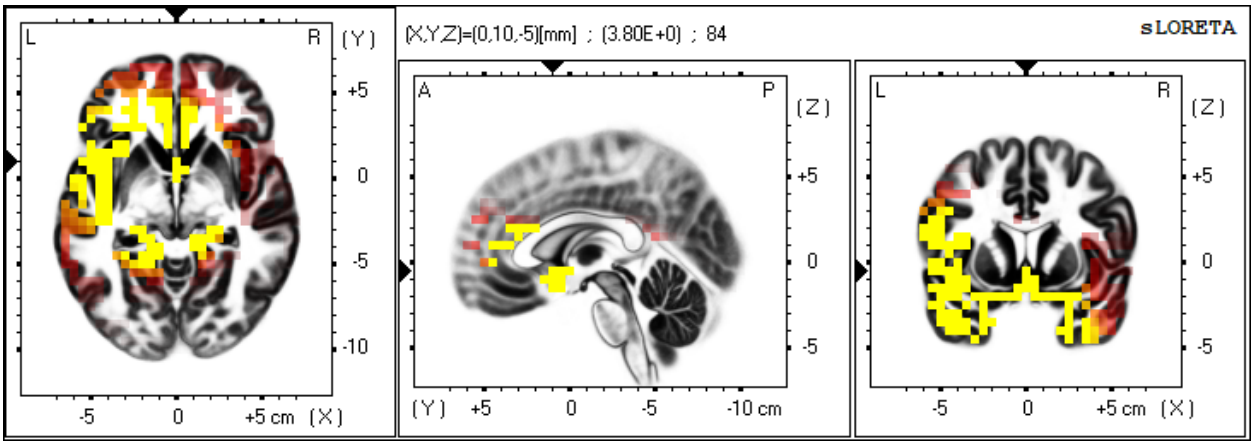

Figure 10. The 33.87Hz source localization represented in transverse, sagittal and coronal slices showing subcortical extent of findings.

Most striking among the data was the appearance of a 33.87 Hz localization including the left temporal lobe, Brodmann area 38 which according to NRF is always injured in ME/CFS patients (Hyde, 2017). The aggregate of 45 ME/CFS brains has also reiterated the hypoperfusion in

Broca's area found in this individuals SPECT. Additionally, the left insula, a frequent NRF SPECT finding is significant as shown in transverse section by Figure 10 (Hyde, 2017). The remaining hypoperfusion over the prefrontal, somatosensory on SPECT is partially reiterated; it should be kept in mind that NRF findings have shown the remaining patchy hypoperfusions to be individually variable (Hyde, 2017). Further, this variability in affected cortical areas provides a rational framework to understand the highly protean nature of individual symptomology among the epidemics documented in the first half of the last century (Gilliam, 1938, Sigurdsson et al, 1950).

What Symptomology is Supported Neuroanatomically?

Significant findings in the insula support findings with right sided visceral body sensation including the pain and paresthesia's documented starting in the first half of the last century (Dupont et al, 2003, Gilliam, 1938, Sigurdsson et al, 1950). The medial region of the transverse temporal gyrus beneath the temporal operculum is known to represent vestibular sensation and supports previously documented balance disturbances in ME/CFS (Kahane et al, 2003, Gilliam, 1938, Sigurdsson 1950). The inferior-lateral edge of the left sensory and motor cortices is also reiterated, supporting contralateral pain and paresthesia over the face and within the mouth, as well as impaired movement of the face, tongue and jaw including difficulty swallowing. Trouble swallowing is a classical indicator of neurologic disease (Garouette, 1987, Weiner & Levitt, 1987).

Heschyl's gyrus and Wernicke's area are known to hold the brains primary tonotopic map and are the primary site of language comprehension in most humans; disturbances in these regions are highly correlated with receptive aphasia where incoming information both spoken and written is no longer intelligible to variable degrees (Weiner & Levitt, 1989). These are common NRF findings in ME/CFS (Hyde, 2017). Correspondingly, disturbances in Broca's area are indicators

of expressive aphasia, where spoken and written language can no longer be expressed with correct syntax or fluidity (Weiner & Levitt, 1989, Embick et al, 2000). This is also a common NRF clinical finding here supported by qEEG (Hyde, 2017).

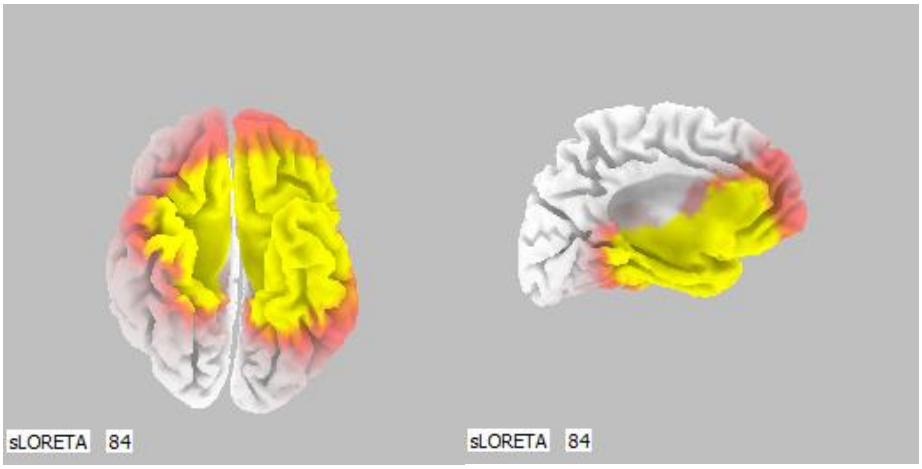

Figure 11. The 33.87Hz localization shown inferior & medial views.

Inferior view of the SLORETA map shows the left fusiform gyrus is also affected. Left hemispheric disturbances in this region are known to be essential for the visual aspects of reading fluency, i.e. transcribing abstract symbols into visual percepts and is included among the ME/CFS cognitive deficits (McCandliss et al, 2003, Hyde 2017). Close by, the left uncus shown in transverse section in Figure 10 receives primary olfactory fibers and disturbances here support the phenomenon of olfactory hallucinations NRF documents in ME/CFS (Garouette, 1987, Hyde, 2017).

Finally, the memory disturbances inherent in ME/CFS are supported by the inclusion of the medial left temporal lobe in general and especially the left hippocampus (Garouette 1987). Lesions in this area have long been associated with the impairments of both immediate and delayed memory recall as exemplified in Alzheimer's dementia (Kohler, et al, 1998). Specifically, the left

hippocampus is associated with memory of spoken words termed verbal memory, and episodic memory i.e. recall of sequentially ordered events (Stepankova et al, 2004). Further, memory consolidation i.e. the assembly of information to be encoded is directly influenced by arousal of the amygdala which is shown here to be hyperactive suggesting that even if memory encoding was intact the information itself is electrically disrupted (LaBar & Phelps, 1998).

The Right Temporal Lobe

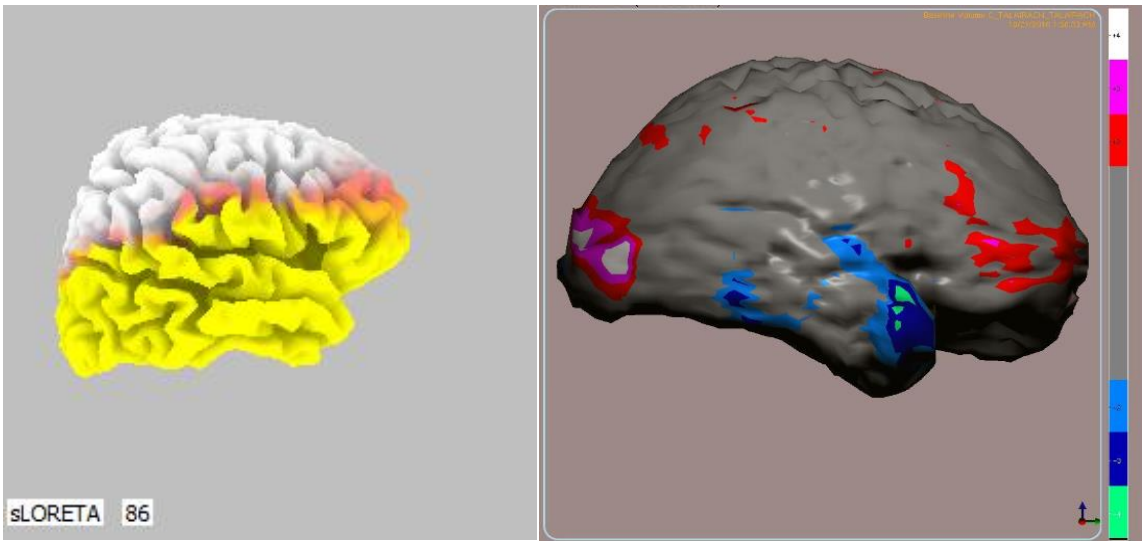

Figure 12. The 34.65Hz source localization compared to a typical right hemispheric NRF ME/CFS SPECT map.

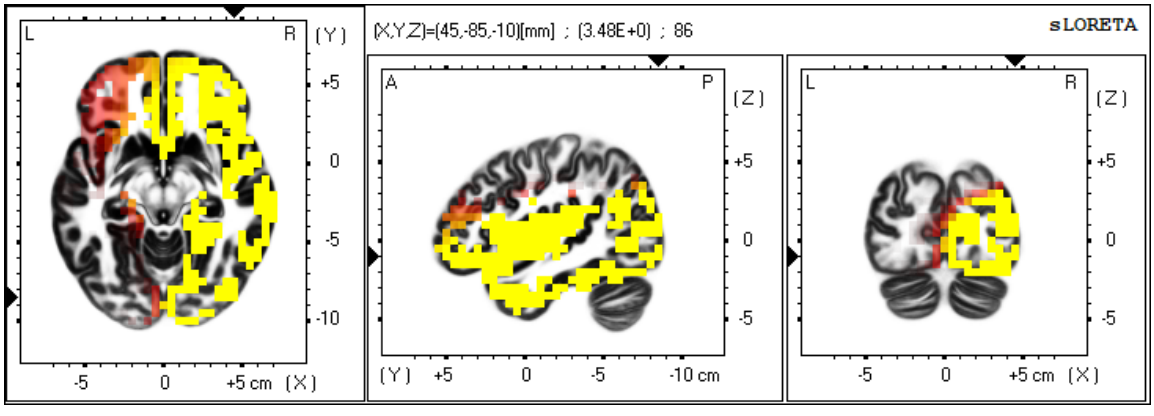

Figure 13. The 34.65Hz source localization represented in transverse, sagittal and coronal slices showing subcortical extent of findings.

The right temporal lobe is an extremely common, though not ubiquitous NRF SPECT finding in ME/CFS (Hyde, 2017). Above in Figure 12, regions of hyper and hypo-perfusion in the frontal, temporal and occipital cortices in this individual's SPECT approximately cover the inferior half of the right hemisphere. Likewise, the SLORETA aggregate of 45 brains includes approximately the same area. Significant areas in the right temporal lobe include the insula, medial vestibular area, inferior-lateral portions of the somatosensory cortices' fusiform gyrus, Heschl's gyrus, Wernicke's areas, Broca's area, uncus, and hippocampus. Additionally, the right occipital lobe is included suggesting primary visual disturbances as explained below.

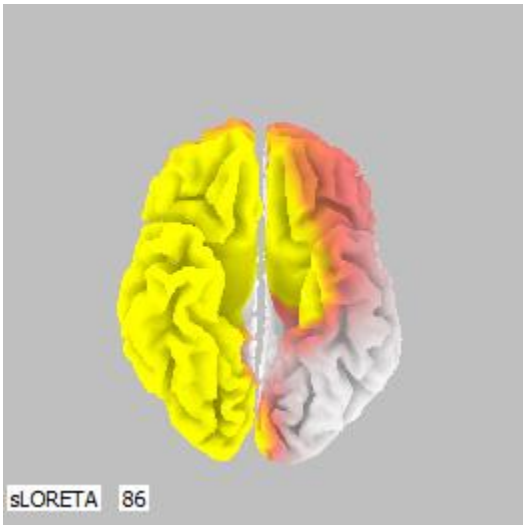

Figure 14. The 34.65Hz source localization, inferior view.

What Symptomology is Supported Neuroanatomically?

Disturbances in the right insula support the same visceral somatic disturbances including pain and paresthesia on the left side of the body (Dupont et al, 2003). The medial region of the right transverse temporal gyrus beneath the temporal operculum representing vestibular sensation is demonstrated, supporting impairments in vestibular sensation and balance (Kahane et al, 2003, Gilliam, 1938, Sigurdsson 1950). The right fusiform gyrus, in contrast to its left hemispheric

counterpart is highly correlated with prosopagnosia - the inability to recognize faces and represents a common NRF finding in ME/CFS (Barton et al, 2002, Hyde, 2017).

Inferior-lateral edges of the right sensory and motor cortices are demonstrated, supporting experience of contralateral pain and paresthesia over the face and within the mouth as well as motor impairments of the face, tongue and jaw including difficulty swallowing (Garouette, 1987, Weiner & Levitt). Disturbances of the right Heschyl's gyrus and Wernicke's area are known to impair recognition of tones received in the contralateral ear (Kimura, 1961). Acquired tone deafness is documented by the NRF, representing one of the more subtle but measurable aspects of ME/CFS (Hyde, 2017). While functional significance of the right hemispheric Broca's area is still being investigated there is evidence to suggest that its abnormal activation is associated with persisting expressive aphasia secondary to lesions in the left hemisphere (Belin et al, 1996, Raboyeau et al, 2008). Additionally, there is evidence supporting that speech prosody, i.e. intonation and patterns of word emphasis and speech gesturing are all supported by the right hemispheric Broca's area (Ross and Mesulam, 1979).

The right uncus receiving ipsilateral primary olfactory inputs is demonstrated, again with its left hemispheric counterpart above supporting NRF's findings of olfactory hallucinations (Garouette, 1987, Hyde, 2017). The nearby hippocampus again represents the essential structure for memory formation, with the right hemispheric known to be specifically correlated with spatial memory meaning impairments here can literally leave a person lost in 3D space (Abrahams et al, 1997). Additionally, moments of insight where new ideas burst forth into consciousness are known to be correlated with the right hippocampus representing a significant reduction in problem solving ability and creativity (Luo & Niki, 2003).

The Right Occipital Lobe

In NRF's 1992 textbook a variety of visual disturbances are described by Dr. Alfredo Sadun, representing some of the least discussed facets of the ME/CFS symptom picture (Hyde et al, 1992). NRF documented visual disturbances include blurring of vision, depth perception and oscillopsia, a commonly seen symptom in clinical neurology where stationary objects may appear to "shimmer", or jump (Hyde et al, 1992, Bender, 1965). Likewise, activity in the lateral occipital cortex as demonstrated in Figure 12 above is known to be specifically involved with disorders of 3D volume perception, i.e. the 3D world represented on the 2D retina (Moore & Engel, 2001).

Vascular disturbances of the occipital lobe are clinically associated with blurring of vision and known to be detectable with EEG again supporting this common finding in ME/CFS (Zunker et al, 2002, Hyde et al, 1992). Moreover, the right temporal lobe is known clinically to be associated with global visual processing including the ability to pay selective attention to abstract forms, specific details of forms and abstract patterns generally (Doyon & Millner, 1991). Additionally, the accurate perception of spatial relationships *between* separate forms is highly correlated with right hemispheric disturbances including the occipital-parietal complex (McFie et al, 1950).

Additional Right Temporal Lobe

5 additional source localizations reiterated the same right hemispheric temporal lobe structures but excluding most of the occipital and frontal cortices. Discovering possible reason(s) for the preponderance of findings in the right temporal lobe is a direction for future inquiry.

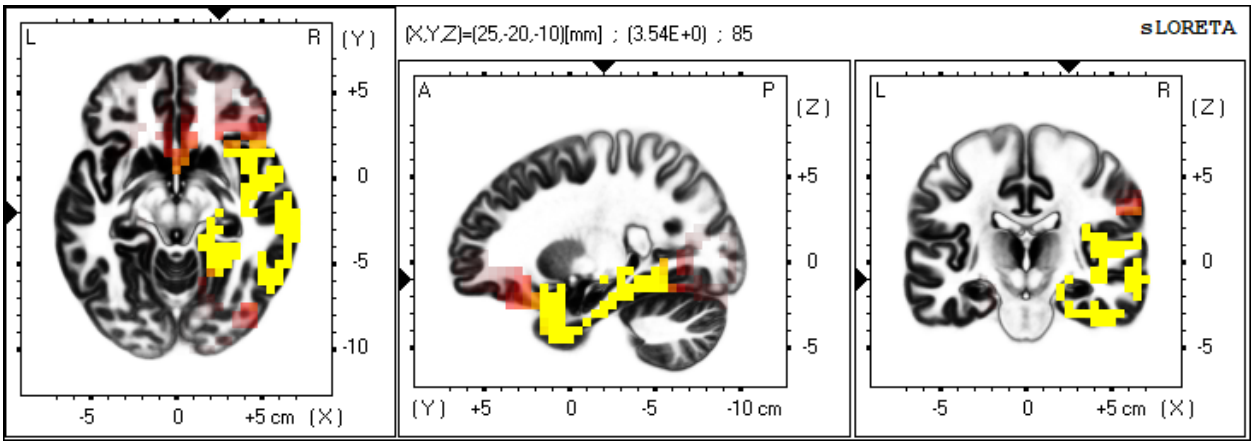

Figure 15. The 34.26Hz source localization represented in transverse, sagittal and coronal slices.

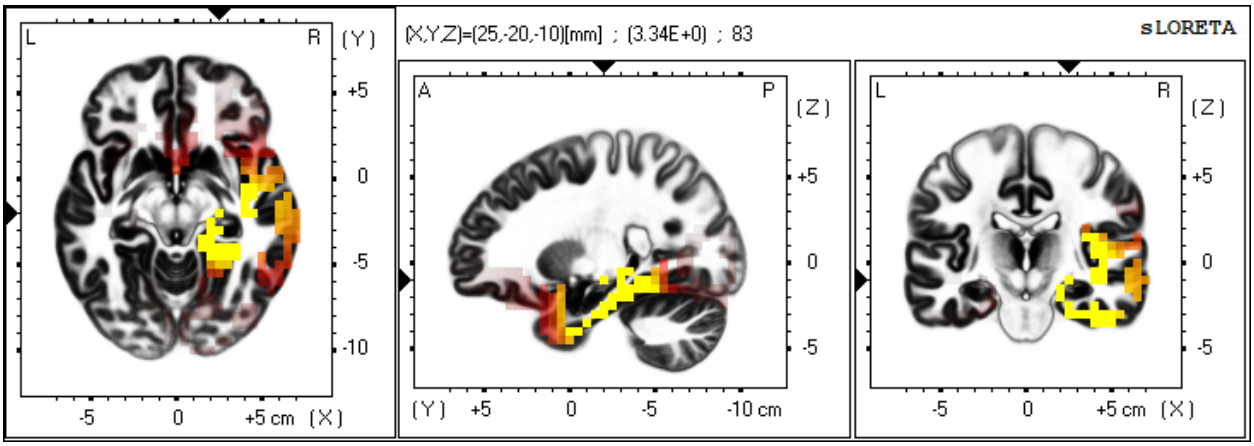

Figure 16. The 33.48Hz source localization represented in transverse, sagittal and coronal slices.

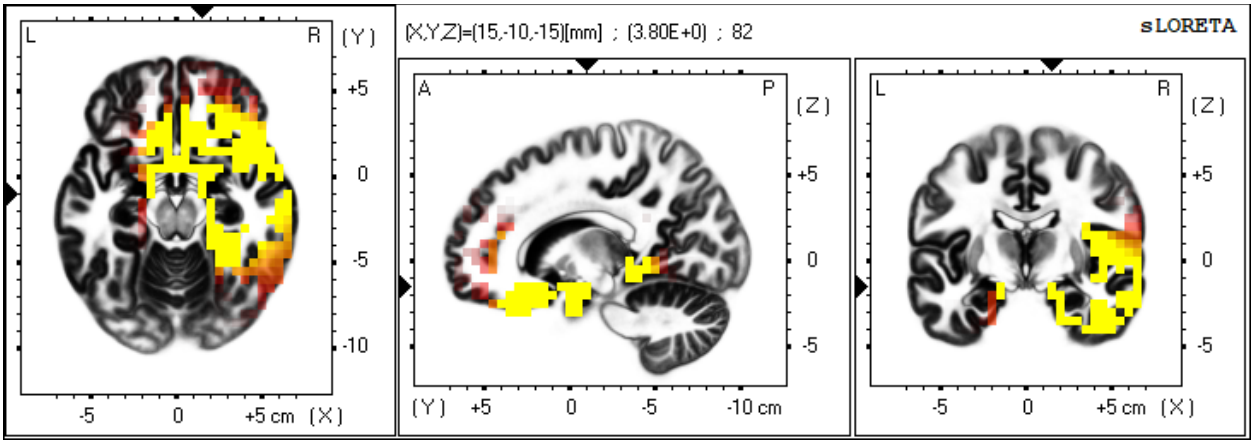

Figure 17. The 33.09Hz source localization represented in transverse, sagittal and coronal slices.

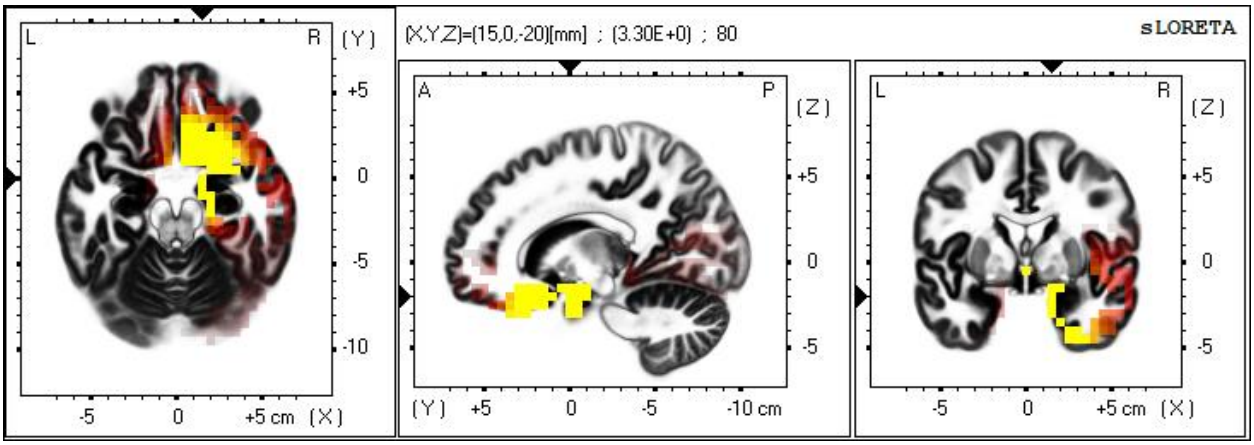

Figure 18. The 32.31Hz source localization represented in transverse, sagittal and coronal slices.

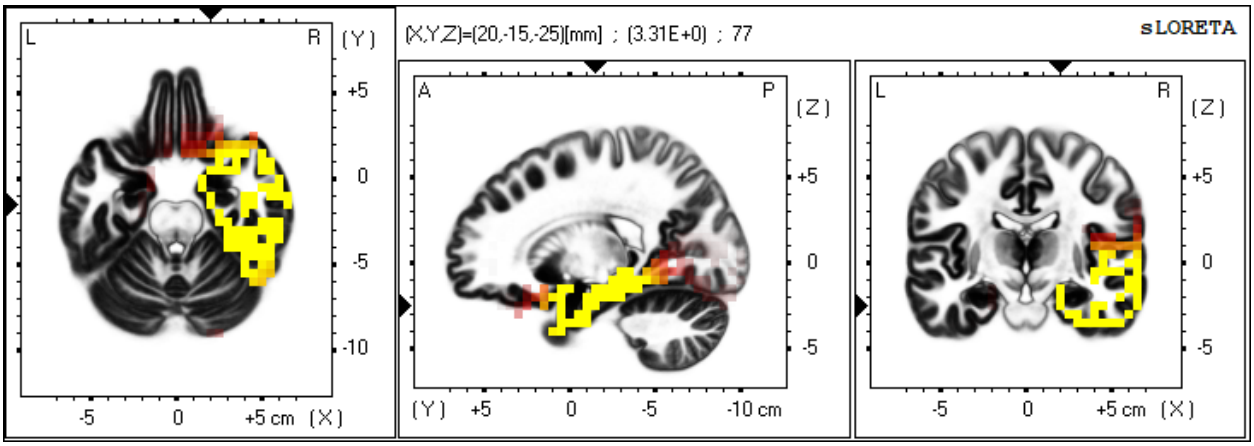

Figure 19. The 31.14Hz source localization represented in transverse, sagittal and coronal slices.

Bilateral Cingulate Cortices

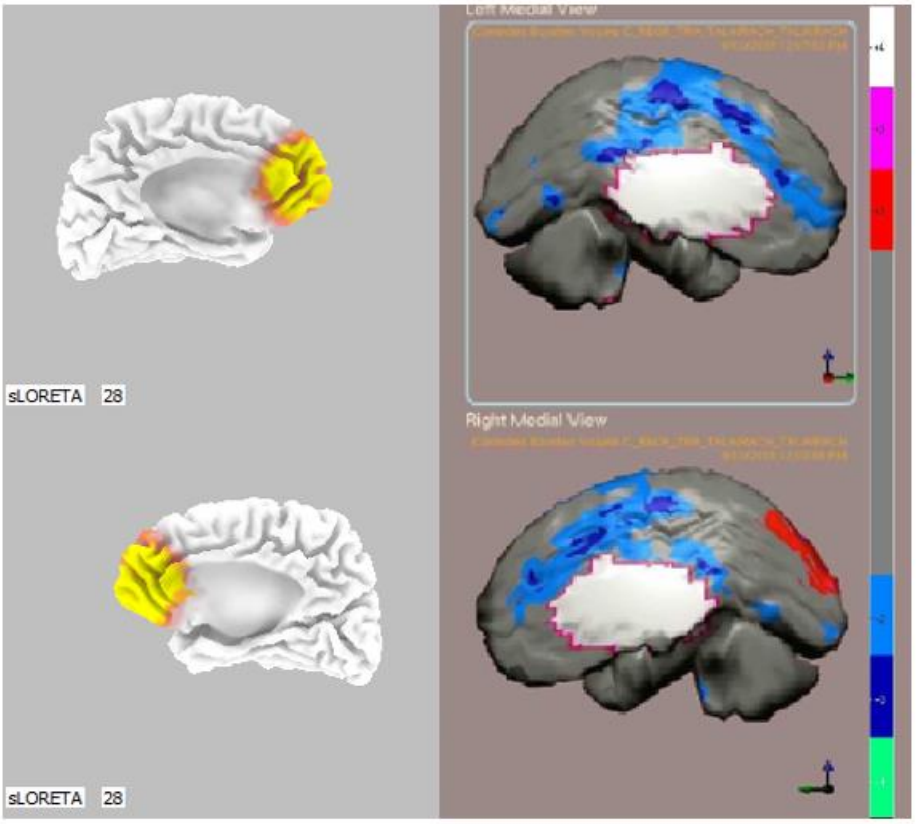

Figure 20. The 12.03Hz bilateral anterior cingulate source localization reiterating approximately the anterior half of this individual's SPECT which also includes the posterior cingulate. Significant areas are confined to the medial portion of the hemisphere.

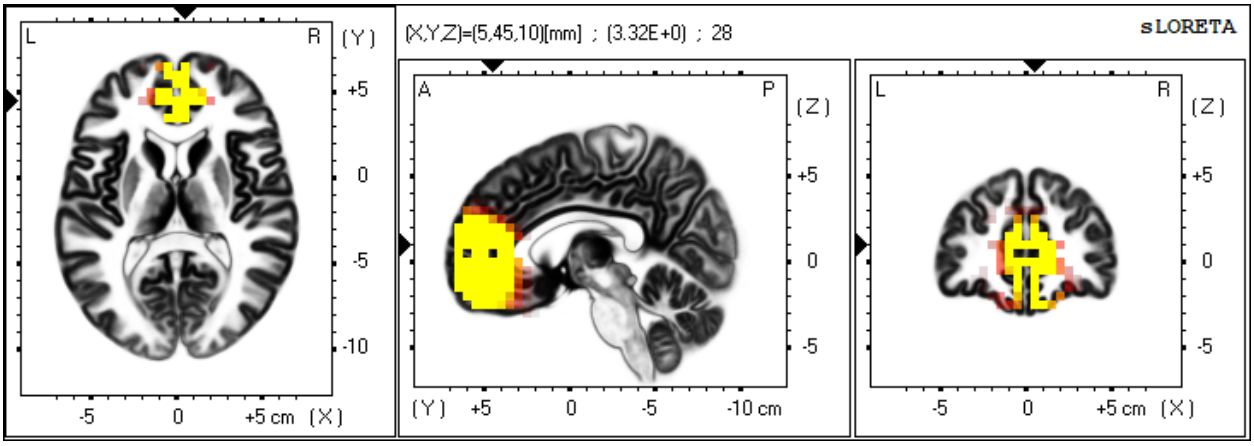

Figure 21. The 12.03Hz source localization represented in transverse, sagittal and coronal slices.

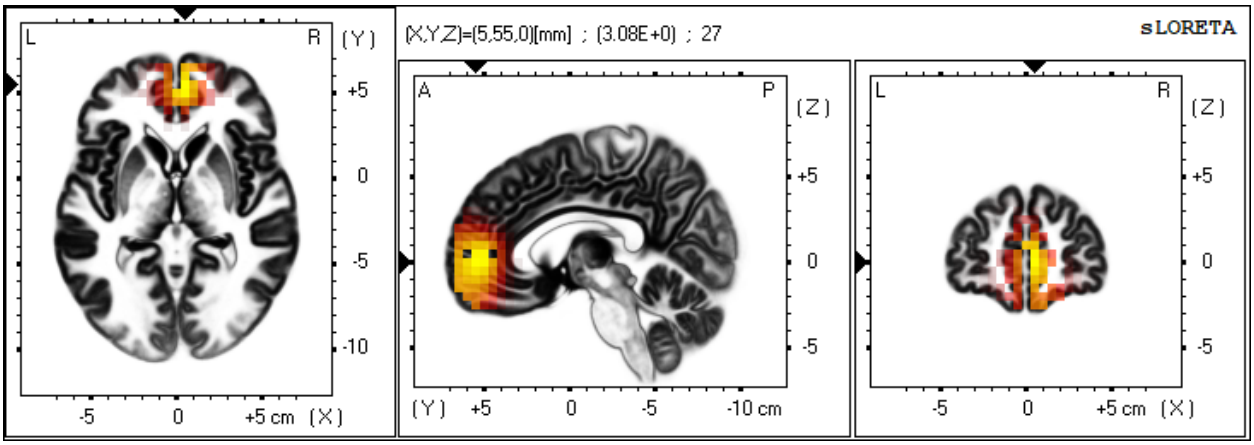

Figure 22. The 11.64Hz, the second anterior cingulate source localization reiterates essentially the same area as Figure 22 above.

What Symptomology is Supported Neuroanatomically?

The anterior portion of the cingulate gyrus is known to anatomically represent experience of emotion including emotional pain and is also associated with cognitive control of expression (Shakman et al, 2011). The anterior cingulate may be divided anatomically into cognitive and affective divisions with the cognitive aspect localized superior to the corpus callosum over the medial surface and the affective portion localized beneath over the medial surface (Bush et al, 2000). Both areas are represented in the 12.03Hz source localization in Figure 21 above with a majority in the affective division. Moreover, general arousal, conflict monitoring and response selection to a given situation are highly correlated with anterior cingulate function, representing a viable explanation for the emotional lability documented in the early part of the century (Swick & Jovanovic 2002, Gilliam, 1938, Sigurdsson 1950).

Of particular interest among future directions is review among the individual brains composing the aggregate to see if perhaps significantly increased and decreased activity among individuals cancelled out what would otherwise have reiterated findings in the posterior cingulate cortices.

Bilateral Pre-frontal Cortices

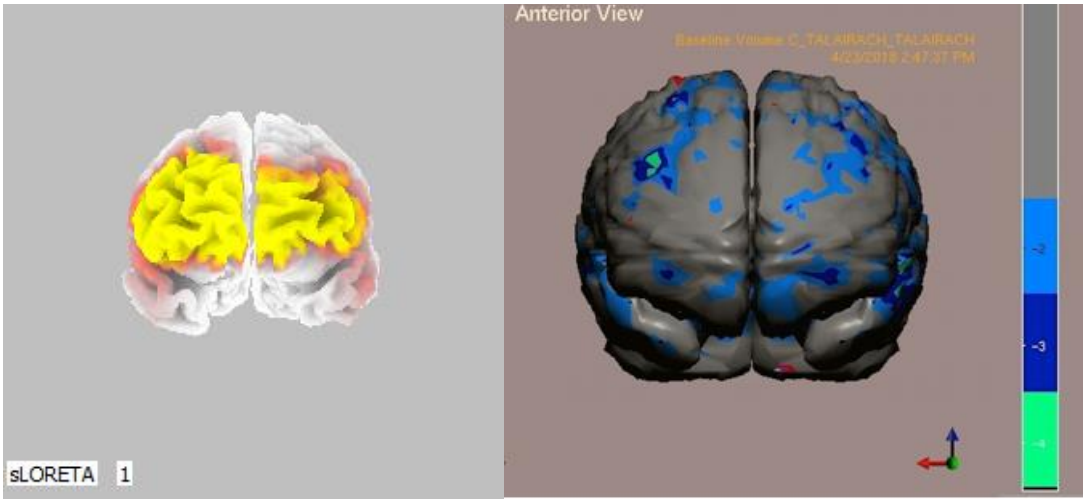

Figure 23. The 1.5Hz source localization corresponds with individually variable NRF SPECT patchy hypoperfusion over the prefrontal cortices.

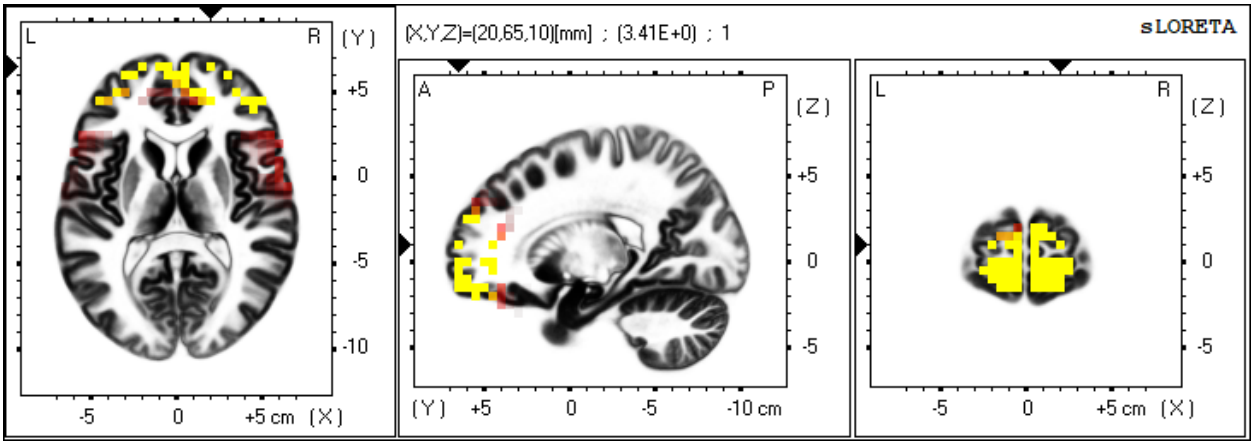

Figure 24. The 1.5Hz source localization showing subcortical extent of findings.

What Symptomology is Supported Neuroanatomically?

The prefrontal cortices are known to be among the most highly susceptible cerebral sites to injury and commonly seen in clinical neuropsychological practice (Stuss & Levine, 2002). Broadly speaking the prefrontal cortices of both hemispheres are known to be essential for the wide variety of executive cognitive faculties essential to navigating complex tasks including working memory, sustained attention to external and internal reference points, attention switching, selective

attention, i.e. being able to focus on something specific in the presence of other stimuli, emotional regulation and associated decision making (Stuss & Levine, 2002).

The Absence of Hypoactivity

Neurons in general and regarding EEG can be grouped broadly as excitatory, representing both the nuclei and Brodmann areas which are the functional subunits of the cerebrum, and the smaller GABAergic inhibitory interneurons which are found distributed in smaller numbers throughout the micro-circuitry of the cerebral cortex (Markram et al, 2004). The electromagnetic language of the brain represented in binary as 1's and 0's in terms of action potentials depends on a chaotic but homeostatic interplay between excitatory and inhibitory activity such that an injury to one subset or the other can deregulate potentially any cerebral process (Vreeswijk & Sompolinsky 1996). Between 70-80% of cortical neurons are excitatory, while the remaining 20-30% are inhibitory (Markram et al, 2004). Despite smaller size and numbers of inhibitory interneurons their essential role is the coordination of all cerebral activity, and directly dependent on glucose received from blood (Persinger, 1995, Kepecs & Fishell 2014).

Given the overlap with NRF SPECT findings and distribution of inhibitory interneurons throughout the cerebral cortex combined with the relative paucity of oxygen available even in healthy brains it appears possible that the hyperactivity characterizing qEEG findings arises from loss or impairment of the inhibitory neuron network secondary to insufficient vascular supply (Markram et al, 2004, Hampson et al, 1990).

Given that inhibitory interneurons do not generally project into the large white matter tracts one can infer as described above that the basic picture of impairment will first be relatively localized as discussed above (Markram et al, 2004). Secondly, arising from the reception of deregulated

signals the frontal lobes *even if* relatively uncompromised themselves remain a loss for intact afferent information via the longitudinal white matter tracts leading to impairments of coordination and sustained attention, creating a general disorientation (Crosby et al, 1962). The especially strong dependence of the hippocampi on interneurons is illustrated by work showing that as many as one thousand excitatory neurons can depend on a single inhibitory interneuron to function normally, highlighting a powerful destructive effect on memory with even minimal neuron loss (Cobb et al, 1995).

Significance

It appears highly likely that the vascular cuffing phenomenon arising from enteroviral infection in poliomyelitis and it's associate ME in the early part of the last century remains alive and well in the world today with the latter enjoying the benefits of being overlooked or conflated with the nonsensical CFS definitions and their offspring by the general medical profession. Despite this, essential data describing the basic nature of ME have been increasingly well developed by the dedicated and insightful work of a small handful of experienced physicians and researchers.

Contrary to erroneous assumptions that ME cannot be measured, or is defined solely by subjective fatigue, the evidence herein shows that reliable empirical measurement is possible right now with the use of appropriate functional brain imaging technology. This includes SPECT and now qEEG in combination with sLORETA software. Both modalities strongly support the historical record of symptomology going back to 1934 as told by the neurons and blood cells themselves.

Of special relevance is the non-invasive, inexpensive and common nature of EEG technology which furnishes even the most technologically limited researchers and especially medical professionals' ready means to get a first-hand look at the definitive features of a scourge that has

lasted nearly a hundred years. It is the authors sincere hope that the present study can be of immediate practical assistance in bringing this unique phenomenon out into the light where many more will use the tools described herein as the starting points to finally end the suffering created both by the enteroviral encephalopathy ME and the aberrant CFS construct which has no place in the modern world.

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Appendix A

NRF Permission Letter

The Nightingale Research Foundation

Byron M. Hyde, M.D.

121 Iona St.

Ottawa, Ontario

Canada

K1Y 3M1

www.nightingale.ca

Tel. private # (613) 729-8995 / fax (613) 729-0148

Charitable Registration No.: 0810341-11

April 4, 2019

To Andrew Pellegrini,

Laurentian University, Sudbury, Ontario

Dear Andrew, It is with great pleasure I give you permission to use any text or illustrations in any of my publications for your thesis, slides or presentations.

If any further documentation is required I shall be back in Ottawa after the 12th of April 2019, but should be reachable by email at any time.

Please also give my best wishes to your parents.

Sincerely,

Appendix A

NRF Permission Letter Cont.

Byron M. Hyde M.D.

Byron M. Hyde MD

Appendix B

Laurentian Ethics Approval Certificate

APPROVAL FOR CONDUCTING RESEARCH INVOLVING HUMAN SUBJECTS

Research Ethics Board – Laurentian University

This letter confirms that the research project identified below has successfully passed the ethics review by the Laurentian University Research Ethics Board (REB). Your ethics approval date, other milestone dates, and any special conditions for your project are indicated below.

TYPE OF APPROVAL / New **X** / Modifications to project / Time extension

Name of Principal Investigator and school/department	Andrew Pellegrini (PI), Faculty of Arts/Psychology; Michael Persinger (Supervisor), Kevin Soroka & Max Lakanen (Co-investigators)
Title of Project	A Quantitative Electroencephalographic (QEEG) Investigation of ME/CFS Patients
REB file number	6011066
Date of original approval of project	May 20, 2018
Date of approval of project modifications or extension *(if applicable)*	
Final/Interim report due on: *(You may request an extension)*	May 20, 2019
Conditions placed on project	

During the course of your research, no deviations from, or changes to, the protocol, recruitment or consent forms may be initiated without prior written approval from the REB. If you wish to modify your research project, please refer to the Research Ethics website to complete the appropriate REB form.

All projects must submit a report to REB at least once per year. If involvement with human participants continues for longer than one year (e.g. you have not completed the objectives of the study and have not yet terminated contact with the participants, except for feedback of final results to participants), you must request an extension using the appropriate LU REB form. In all cases, please ensure that your research complies with Tri-Council Policy Statement (TCPS). Also please quote your REB file number on all future correspondence with the REB office.

Congratulations and best wishes in conducting your research.

Appendix B

Laurentian Ethics Approval Certificate Cont.

Susan Boyko, PhD, Vice Chair, *Laurentian University Research Ethics Board*

Appendix C

Recruitment Script

Laurentian University Behavioural Neuroscience Program

Seeking Volunteers for

Research into

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Approved by Laurentian University Review of Ethics Board (LUREB) file #: 6011066

We are a team of academic researchers working under Dr. Michael Persinger, head of the Behavioural Neuroscience program at Laurentian University.

We are seeking adult volunteers (18 and over) from the Toronto area with a medical diagnosis of Myalgic Encephalomyelitis/Chronic fatigue Syndrome (ME/CFS) to participate in a non-invasive neuroscientific investigation of brain functioning.

Of special interest is anyone diagnosed by Dr. Byron Hyde of the Nightingale Research Foundation (NRF) based on Single Positron Emission Tomography (SPECT), and gastric biopsy test for persistent enterovirus presence.

Our interest is in using Quantitative Electroencephalography (QEEG) to evaluate features of brain activity in ME/CFS compared both to healthy controls, and features of ME/CFS discovered in NRF's SPECT research.

Our intention is to build empirical support for ME/CFS as a distinct and identifiable illness that can be observed with relatively inexpensive, safe tools that are commonly available.

What Does Participation Involve?

Participants will be visited in their homes by two researchers who will take measurements of brain electrical activity or "brain waves" using QEEG.

Appendix C

Recruitment Script Cont.

QEEG is a safe, painless and non-invasive technology that records brain activity using a cap containing special sensors placed on the head. A small amount of conductive gel is added to the sensors, and we suggest participants may wish to plan for washing their hair after the researchers visit to remove residue.

Data Collection Procedure

Participants will be asked to sit upright for around 30 minutes in a comfortable back supporting chair inside a dark, quiet room somewhere in their home while wearing the cap. Relative darkness and silence will ensure the best measurements possible using QEEG.

Participants will be asked to sit with their eyes open, eyes closed, and to complete a simple breathing task that will be explained by the researchers.

A short questionnaire will also be conducted to gather information about general features of ME/CFS related to each participant.

The entire in-home visit is expected to be no more than forty-five minutes to an hour.

The researchers acknowledge that persons with ME/CFS may be experiencing significant disability. We wish to emphasize that home visits will be conducted with the utmost respect, and specific attention to the comfort of participants.

This Research is Independent of Medical Care

It must be noted that no one on our research team is a physician, and that participation in this study is separate from any form of medical care or diagnosis.

Consent & Privacy

Interested persons will be required to complete a consent form prior to participating that can be received by emailing the address below.

Anonymity will be strictly maintained for participants. All data collected will be kept completely confidential and stored in a secure location accessible only to members of our research team.

Scheduling & Contact Information

We plan to visit Toronto sometime during the summer of 2018. Specific appointment times will be made by email according to what is most convenient for participants.

Appendix C

Recruitment Script Cont.

Anyone interested is welcome to contact apellegrini@laurentian.ca to receive a copy of the consent form or request additional information.

Appendix D

Consent Form

I _____, agree voluntarily to participate in an exploratory study intended to determine features of brain functioning associated with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

During the study my electroencephalographic measurements or "brain waves" will be measured using the quantitative electroencephalograph (QEEG). Information about ME/CFS will also be obtained by answering a brief questionnaire.

The entire visit from the researchers is expected to be no longer than half an hour to an hour.

QEEG Procedure

The researchers have told me that QEEG is a safe, non-invasive procedure that requires me to sit for approximately 30 minutes with a cap on my head. The cap contains 19 sensors that will monitor my brain activity when my eyes are open, when my eyes are closed, and when I engage in a breathing task explained to me by the researchers.

Purpose & Potential Benefits to Participants

I understand the purpose of the study is to examine the brain activity of individuals with a medical diagnosis of ME/CFS to see if they differ from individuals without the condition.

I understand this is an exploratory study, that will not directly benefit me in any way. I understand that people with ME/CFS in the future may benefit from my participation in this study, if it leads to an accurate and efficient method of diagnosis, or provides additional insight into ME/CFS features.

Confidentiality

All information obtained from this study will be kept strictly confidential and will be maintained in a secure laboratory protected by three metallic doors. Digital information will remain on a password-protected computer stationed permanently within the laboratory. Only the principal supervisor Dr. M. A. Persinger, Dr. Kevin S. Saroka, and the researchers Andrew Pellegrini, and Max Lakanen may access the information.

Participant Access to Study Data

Appendix D

Consent Form Cont.

At completion of the study, I may obtain a report from the researchers detailing my own brain profile that I may choose to share with medical professionals. This report will be provided to me for information only; it is not guaranteed to be accurate or useful.

Additionally, I may choose to receive a one-page summary of the study findings sent to my email address. Emailed data may be encrypted using Microsoft Word before sending, which I can access by a password of my choice.

In Case of Emergency

If I experience a medical emergency during the researchers visit I understand that I may call 911 for assistance, or that the researchers may do this on my behalf.

If I become distressed for any reason during the researchers visit, I understand that I may ask them to leave, and that the will comply in an immediate, and respectful manner.

Questions & Contact Information

If I have any questions related to this study I may contact the principal supervisor of this study, Dr. M. A. Persinger at (705)-675-4824 or, Dr. Kevin S. Saroka (705)-675-1151 ext. 4564. Laurentian University can be reached toll free at 1-800-461-4030.

I may also contact the Regional Ethics Officer, (Office of research Services, telephone 705-675-1151 ext. 3681), toll free at 1-800-461-4030, or by email at ethics@laurentian.ca, to reach an official not affiliated with the research team regarding any issues.

This Study is Independent of Medical Care

I understand that I am not receiving a medical diagnosis, or medical treatment of any kind by participating in this study.

I understand that Dr. Persinger, and Dr. Saroka are academic researchers, and not physicians. Neither Dr. Persinger or Dr. Saroka will play a role in directly diagnosing my condition, nor will they provide or facilitate access to medical care. I understand that participation in this study is completely independent of my medical care.

Participants Right to Withdraw

I understand that I have the right to withdraw, and have my data removed from the study at any time prior to completion.

Informed Consent

While I have been informed that the risk of any adverse event related to participation in this study is extremely small, I am accepting of all potential risks by agreeing to participate.

Appendix D

Consent Form Cont.

I certify that I am an adult, age 18 years or over at the time of signing this document.

Signature of Subject: _____

Date: _____

Optional Email Address: _____

Optional Encryption Password: _____