THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF PSYCHOLOGY

SUPERFICIAL SIDEROSIS OF THE CENTRAL NERVOUS SYSTEM: A PROPOSAL FOR THE USE OF FUNCTIONAL MAGNETIC RESONANCE IMAGING IN CLINICAL RESEARCH

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Spring 2012

A thesis
submitted in partial fulfillment
of the requirements
for baccalaureate degrees
in Psychology and Science
with honors in Psychology

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Abstract

The goal of the current paper is to document the brain and behavioral changes associated with Superficial Siderosis, and to present a proposal for the use of functional Magnetic Resonance Imaging as a method of studying this disorder. Superficial Siderosis constitutes a rare neurological caused by an increase deposition of hemosiderin (an iron-storing complex) in the pia and arachnoid layers of the meningeal tissue. There is little information linking the basic brain changes associated with Siderosis to behavioral correlates.

Cardinal symptoms of Superficial Siderosis include progressive hearing loss, cerebellar ataxia with myelopathy and dementia/memory impairments. The pathogenesis of this disease occurs in the Bergmann glia and microglia of the cerebellum. While most research concerning Superficial Siderosis focuses on the molecular mechanisms of this disease, few studies focus on the neuronal networks and brain activation associated with this disease. A majority of studies instead utilize static, structural imaging techniques to study Superficial Siderosis, including Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI). The current paper proposes the use of structural and functional imaging, including susceptibility weighted imaging and blood oxygen level dependent functional Magnetic Resonance Imaging (BOLD fMRI) to investigate brain activation in clinical patients with a positive presentation of Superficial Siderosis.

Contents

Introduction

With an estimated prevalence of 625 cases per 100,000 in the population, neurological disorders present a serious issue to the modern community (McDonald et. al., 1996). In the past decade the World Health Organization (WHO) named neurological disorders as one of the greatest threats to public health (*Neurologic Disorders: Public Health Challenges,* 2006). According to the WHO, the more well-known and important neurological disorders include: dementias, epilepsy, headache disorders, Multiple Sclerosis, disorders associated with malnutrition, Parkinson's disease, Stroke and Traumatic Brain Injury (*Neurologic Disorders: Public Health Challenges,* 2006). Therefore, this organization and many others have focused their efforts on examining these disorders in detail, with the result that most of these disorders are well known, and already have an established literature base.

However, with the increased attention on these more salient disorders, there is a sacrifice towards the less-common disorders. With health impacts that often rival those of the more common disorders, these syndromes require just as much research as any other. One such disorder is Superficial Siderosis of the Central Nervous System (SS). For years known as a rare neurological disorder, with the advent of more modern imaging technologies the known prevalence of this disorder is increasing (Kellermier et. al., 2008). Originally described almost 100 years ago, it wasn't until Magnetic Resonance Imaging (MRI) that the disorder was described in greater detail. Before the use of MRI the disorder could only be definitively diagnosed post-mortem (Aichner et. al., 1993).

SS is a condition that results from wide spread deposition of hemosiderin around various regions in the central nervous system, most notably the subpial layer (Miele et. al., 2005).

Hemosiderin is a product of the degradation of blood, in which hemoglobin is broken down into heme, which eventually is converted into hemosiderin (McClatchey, 2002).

The effects of the disorder do not reach the peripheral nervous system. Instead, the hemosiderin deposits cause a variety of neuropathological damages in the CNS, most notably gliosis, neuronal loss and demyelination (Fearnley et. al., 1995). These depositions occur mainly on regions located in the hind brain, and are rarely found in significant amounts in the forebrain (Schmahmann et. al., 1998). The pathogenesis of this disease occurs in the Bergmann glia and microglia of the cerebellum (Koeppen et. al., 1993) and an estimated 50% of cases are due to an brain hemorrhages of uncertain causes, also known as chronic subarachnoid hemorrhages. The other half of established cases generally arises due to a subarachnoid hemorrhage that has a known cause such as tumor, arteriovenous malformation, traumatic brain injury (Levy, Turtzo & Llinas, 2007) as well as amyloid angiopathy and Brachial plexus/root injury (Miel et. al., 2005)

SS represents a very serious neurological disorder, one that manifests a wide range of symptoms. Due to the current lack of knowledge concerning this disorder, it is often initially misdiagnosed as simply a sub-arachanoid hemorrhage or Multiple Sclerosis (Levy et. al., 2007). According to Levy et al., 2007 an estimated 35% of all SS cases are categorized as idiopathic.

As mentioned previously, current research has established that a history of head trauma is a common theme among individuals presenting with SS. Intradural surgery has also been linked to a greater risk of developing the disorder (Dubessy et. al., 2011). Additionally, one case study indicated that aspirin therapy can lead to the development of the disorder. However, once the patient ceased using the aspirin at therapeutic doses, his symptoms became stable (Dubessy et. al., 2011).

The symptoms of SS can be grouped into four major categories: Sensory, Motor,

Cognitive and Speech. While the disorder is mainly characterized by hearing loss (sensory), ataxia (movement) and dementia (cognitive), many of the other symptoms occur as the disorder progresses. The following section will fully describe a majority of the symptoms presented in the reviewed case studies.

Hearing Loss

One of the primary symptoms present in SS is hearing loss, also referred to as sensorineural hearing loss (Lemmerling et. al., 1998). Hearing loss is estimated to be present in almost 95% of all cases (Vibert et. al., 2000) This deficit is often one of the first complaints of patients, and is frequently the first symptom that brings them in for diagnosis. Current research has postulated that this sensorineural hearing loss is due to damage to the vestibulocochlear nerves, which are covered by a low-signal intensity material, caused by the hemosiderin deposits. In their case study, Vibert et. al., 2000 notes that MRI is the preferred imaging method to study superficial siderosis, in particular for those individuals with bilateral cochlea-vestibular deficits (Vibert et. al., 2000).

Tinnitus

Another hearing deficit present in SS patients is tinnitus, or an auditory perception that is not due to any physical cause (Nicholas-Puel et. al., 2002). This disorder is also present in many other neurological disorders, such as Multiple Sclerosis and Traumatic Brain Injury. Generally, this disorder is found to be a deficit of the cochlea. It is hypothesized that tinnitus is due to the auditory pathway's interpretation of spontaneous signals as actual auditory sounds. In general, as there is no definite cure for this symptom, patients are often encouraged to attempt to manage their symptoms.

However, through their study of the neurophysiology of this symptom, Jastreboff and colleagues were able to develop a preliminary method for treating tinnitus. In their method, patients were taught techniques to acquire a habituated state towards their tinnitus symptoms, only becoming aware of the auditory perceptions when they chose to (Jastreboff, Gray & Gold, 1996).

Anosmia

Anosmia (or hyposmia) refers to the inability to use the olfactory senses. In the case of SS, this symptom is a very common one. However, as the olfaction senses are rarely tested in either clinical or research settings, this symptom is highly underreported (Kumar, 2007). Studies of the neuropathology of SS have shown that the inferior frontal lobes are often damaged by this disorder, which could be a factor in the development of anosmia (Van Harskamp et. al., 2005).

In individuals with head trauma, anosmia occurs in about 5% of all cases (Mann, 2006). Mann, 2006 investigated the SPECT and MRI findings of anosmia due to head trauma. It was found that even if the anatomic images from the MRI were negative for clinical findings, the SPECT scans demonstrate abnormal findings. According to Mann, 2006, anosmia has a varied etiology. This symptom can result due to damaged nasal passages, sinuses, or both resulting in an actual mechanical block of odorants; the tearing of olfactory axons as they travel over the cribriform plate, or even direct damage to the bulb and destruction of the olfactory regions located in the cerebral cortex (Mann, 2006).

The findings from this study indicate that a functional method (such as SPECT imaging) can help to augment the findings from a structural method, as was the case with the MRI scan. While the structural/anatomical images may present as negative for clinical symptoms or damage, the functional scans may indicate a deficit previously unknown.

Vision Deficits

In addition to hearing and olfactory sensory deficits, SS patients present with a variety of visual deficits. These deficits occur in an estimated 5 to 10 percent of published cases (Fearnley et. al., 1995). Visual deficits include extraocular nerve palsies in addition to optic and trigeminal neuropathy (Kumar, 2007). Generally, patients experiencing visual problems experience a deficit in visual acuity (Fearnley et. al., 1995).

Cerebellar Ataxia

Ataxia presents as a disorder of coordination, which can affect large and small motor movements, such as of the fingers, toes, arms or legs (*Diagnosis of Ataxia*). This disorder of movement is found is a majority of SS cases, with percentages of over 59% of all cases (Anderson et. al., 1999). The presence of cerebellar ataxia is now one of the main triad of symptoms used in the diagnosis of the disorder, which can aid in a bedside diagnosis (McCarron et. al., 2003).

Generally, MRI scans of patients presenting with cerebellar ataxia show a ring of hypointensity around the regions of the cerebellum, which is indicative of hemosiderin deposits in this area. Prior research has indicated that the cerebellum is one of the major areas affected by SS, in addition to the brain stem and cerebrum, spinal cord, and cranial nerves (McCarron et. al., 2003).

Cognitive Decline

Few studies have investigated the cognitive and neuropsychological functioning of SS (Van Harskamp et. al., 2005). However, current research has established that, in the presence of MRI-demonstrated lesions (especially of the cerebellum) a specific behavioral pattern arises. Before investigating the cognitive characteristics of superficial siderosis, Van Harkskamp et al.,

2005 noted that only dementia had been linked to this disorder.

After completing a matched-control study, Van Harskamp and colleagues were able to illustrate a more complete picture of cognitive and neuropsychological functioning in SS patients. All subjects (n= 6) had a normal verbal IQ at the time of testing. Additionally, verbal recognition, visual recognition memory and recall memory were normal for all of the subjects. On the Rey Complex Figure Test (a test of visual memory and visual construction), all patients save one demonstrated impaired scores, even though they performed at normal levels for the copy condition (Van Harskamp et. al., 2005, Min-Sup Shin et. al., 2006). Executive control, attention, response initiation and response inhibition were also areas of major impairment for the subjects (Van Harskamp et. al., 2005). During theory of mind tasks, the patients performed at below-normal levels, indicating their impaired ability to take another's point of view (Van Harskamp et al., 2005).

Cerebellar damage has been linked to cognitive decline (Schmahmann et. al., 1998). Both anatomical and functional studies have indicated that this brain region is responsible for higher-order functioning (Schmahmann et. al., 1998). As the cerebellum is one of the most negatively affected regions in superficial siderosis, the presence of cognitive deficits in patients comes as no surprise.

Dementia is another symptom that is a results of late-progressive SS. However, this dementia often differs from the characteristic dementing disorders such as Alzheimer's. For example, one 75 year old man was initially referred for continuing memory impairment (Dubessy et. al., 2011). Upon examination, he demonstrated significant mental impairments, such as a score of 16/30 on the Mini Mental State Exam (Dubessy et. al., 2011). Additionally, he exhibited impairments in executive functioning, language skills, and praxis. Therefore, his

profile differed from that usually present in Alzheimer's and other dementing diseases. While patients often initially present with dementia, in the presence of deafness, cerebellar symptoms or pyramidal signs, a diagnosis of SS should be investigated (Dubessy et. al., 2011).

Current imaging methods for Superficial Siderosis

While most research concerning SS focuses on the molecular mechanisms of this disease, few studies focus on the neuronal networks and brain activation associated with this syndrome. A majority of studies utilize static, structural imaging techniques to study Superficial Siderosis, including Single Photon Emission Computed Tomography (SPECT), Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) (Maggioni et. al., 1997). In the following, I provide a review of the few functional imaging methods to date that examine SS.

Positrom Emission Tomography (PET)

While one of the more invasive brain imaging techniques, PET is a useful method for examining in vivo neurometabolism based upon injection of a radioactive tracer. PET has the ability to image receptor-binding and metabolic activity at a molecular level (Mishina, 2008). PET scans can also measure the cerebral blood flow at a region in the brain.

As it is a nuclear imaging method, the patient comes into contact with quantities of radioactive tracers, which are a mix of naturally occurring molecules that bind to a radioactive compound. The radioactive compound varies depending upon the type of imaging data desired. Two of the more commonly used radiopharmaceuticals used in PET research are [15O]CO2, [15O]H2O and [18F]FDG, which measure cerebral blood flow and glucose metabolism respectively (Mishina, 2008). [18F]FDG is often used to study neurological disorders and to aid in their diagnosis. For example, patients with Alzheimer's Disease often present with reduced

cerebral glucose metabolism in both the parietal lobe and the posterior cingulate gyrus (Mishina, 2008).

In PET studies of SS, researchers often use the C-Pittsburgh compound B (PIB) positron emission tomography (PET) imaging technique (Dhollander, 2011). This compound is used in order to locate vascular and parenchymal β amyloid plaques. Dhollander, 2011 indicated that these depositions of β amyloid plaques could lead to a specific signature indicative of SS, in both the clinical realm and with MRI.

Single Photon Emission Tomography (SPECT)

SPECT, another imaging technique, also falls under the category of nuclear medicine imaging. However, instead of using various naturally occurring molecules labeled with radioactive tracers as in PET, SPECT utilizes radioactive compounds that emit gamma rays to create a 3D image (Jaszcza et. al., 1984). This tracer is usually injected directly into the bloodstream, where it can easily reach the brain. These radioactive isotopes are often bonded to a ligand, which has the ability to bind to certain tissue types in-vivo. The image occurs when a scanner picks up on the emitted gamma rays. The gamma-ray camera receives many different 2D images from a variety of angles. It then pieces the series of images together to create a 3D image of the target (Jaszcza et. al., 1984).

Magnetic Resonance Imaging

Since the original experiments of Bloch and Purcell, Magnetic Resonance Imaging (MRI) has greatly expanded and broadened our understanding of human anatomy and function. This technique utilizes the inherent properties of the proton, or the positively charged hydrogen atoms

found in water molecules. These protons, due to their spin, create miniature magnetic fields, and will behave differently within the magnetic field based upon their immediate biological environment.

In an MRI scanner, the subject or patient is immersed in a magnetic field. This magnetic field causes the protons to align, creating a homogeneous field. Once a radio frequency (RF) pulse is applied, the protons are knocked out of alignment. The measurement is based upon the rate that the protons precess back to the original alignment, or B_O. The protons found in different tissue types precess back at different rates, and these rates yield data. An image will have a darker than normal region where there is a tumor (due to the ability of protons to move freely around) or cerebral spinal fluid.

MRI provides a window into the structure of various tissue types. This technique provides a better contrasting image as compared to regular radiography or computed tomography (Edelman & Warach, 1993). In the realm of research, this technique has a wide range of applications, spanning from investigating the diagnosis of neurological disorders such as MS to mapping certain regions of the brain.

Past research has extensively investigated SS through the use of this static imaging technique. Through such study it has been found that SS results in diffuse signal loss around the cerebral hemisphere, as well as the cerebellum, the brain stem and the spinal cord (Offenbacher et. al., 1996). This method of imaging is extremely sensitive to the massive hemosiderin deposits. As mentioned previously, these deposits manifest as hypointensities on T2.

Functional Magnetic Resonance Imaging

Due to the recent advances in the study of this disease through the use of MRI, it would be practical to utilize even more advanced imaging methods such as functional Magnetic Resonance Imaging (fMRI). This technique utilizes the ratio of oxygenated to de-oxygenated hemoglobin, also known as the BOLD (blood oxygen level dependent) signal (Chen & Ogawa). As neural activity occurs in a cerebral region, the increase in activity initially decreases the amount of oxygen in that region. The body quickly overcompensates with a relative rush of oxygenated blood to that region, thus producing the large BOLD signal used in analysis (Chen & Ogawa). Due to its reliance on hemoglobin, this functional method of imaging would aid in the study of SS.

As previously mentioned, to date few (if any) research studies have utilized functional methods to investigate Superficial Siderosis. Therefore, the goals of this current paper are to provide a review of 11 case studies of this disorder, and to propose the use of fMRI as a novel technique for studying this neurological disorder.

Methods

PsychInfo search engine was utilized to conduct the necessary literature searches for relevant case studies. Search strains used were "Superficial Siderosis" and "Superficial Siderosis of the CNS." In 2007, Levy and colleagues conducted an extensive review of the current literature base of case studies published to date on SS of the CNS (Levy et. al., 2007). This year was used a lower limit in order to review more recent and novel case studies.

Using this date as a starting point, case studies were collected for analysis using PsychInfo. Search results provided 11 case studies for review in the current paper. In order to provide a thorough comparison and analysis of the reviewed body of literature, a list of the

symptoms described in each studied was compiled. See Table 1 for a description of the variables collected from each study.

Table 1: Descriptions of Data Collected

Data Category	**Description**
Gender	Male; Female
Age	Years : 20, 21, 22, etc.
Symptoms	Qualitative description of the initial and progressive symptoms that the patient presented with
Imaging	Qualitative description of the brain imaging findings of the reviewed studies

Description of symptom categories

Symptoms were further classified based upon the affected modality. Table 2 provides a description of the symptom categories used.

Table 2: Symptom Categories and Descriptions

Symptom Category	**Description**
Sensory	Loss of vision, hypoacusis, tinnitus, anosmia, etc
Motor	Unsteady gate, cerebellar ataxia, pyramidal signs, etc
Cognitive	Mild cognitive declines, memory issues, personality changes, flat affect, disorientation, slowness of thought, etc
Speech	Slurred speech, aphasias, etc

Results

Case Study 1

The first case study reviewed was a 56 year old woman. Her initial symptoms were a mix of sensory (visual loss), physical (headaches and fatigue) as well as cognitive, in that she experienced a distinct personality change (Kellermier et. al., 2008).

As her symptoms progressed, more of the classic symptoms of SS emerged, such as difficulty walking, blurred vision and memory deficits. Additionally, she experienced tinnitus and atrial fibrillations.

MRI imaging initially showed hypointensity around the spinal cord region (Kellermier et. al., 2008). This was the only imaging available for this patient, as the patient, 8 years after her initial presentation of the disorder, passed away due to a grand mal seizure.

Case Study 2

The patient was a 48 year old man who initially presented with an abnormal gate and walking deficits, as well as subdural hematomas and headaches (Levy et. al., 2007). Additionally, he experienced speech difficulties and memory impairment. The patient's progressive symptoms worsened over a period of 6 months. These symptoms included gate difficulties and chronic subarachnoid hemorrhage.

Imaging results initially revealed the subarachnoid hemorrhage through the use of a CT scan. MRI results showed regions of lower activation (hypointensities) on fluid-attenuated inversion recovery around the areas of the leptomeninges. The MRI scan also showed cerebellar atrophy, and diffuse dural enhancement.

Case Study 3

A 53 year old woman initially presented with symptoms of blurry vision, headaches,

hypoacusis, dizziness, ataxia and subarachnoid hemorrhage (Miele et. al., 2005). The symptoms of blurry vision and headache had increased in severity suddenly over a two day period. She had also experienced cardiac irregularities, as demonstrated by the presence of an artificial mitral valve.

Her initial symptoms warranted a CT scan, which revealed an increase in the density around the fissures and sulci. These results led to a diagnosis of a Fisher Grade I subarachnoid hemorrhage. Her symptoms lessened, and she was discharged from treatment. However, the symptoms reappeared a few months later and a second CT scan was performed. This second scan showed hyperdensities along the pial surface and the basilar cisterns which was considered to be atypical characteristics of simply a subarachnoid hemorrhage.

An MRI scan also showed hyperdensities along the pial surface on T1 images. Additionally, hypointensity were found on T2 images of the pial surface of the cerebellum, cervicomedullary junction, brainstem, spine, and in portions of the cereberal hemispheres.

Case Study 4

This next case study details the condition of a 49 year old male. His first symptoms affected primarily his motor functions. He experienced cerebellar ataxia, an unsteady gate, dysarthria, hearing loss, as well as cognitive impairments such as bilateral Babinski signs (Vale, 2011).

While his CT scan showed no abnormalities, a structural MRI illuminated hemosiderin deposits in the in the midbrain, retrosplenium, mesencephalic tegmentum, and cingulate sulcus.

Case Study 5

Patient number 5 (a 69 year old male) initially presented with symptoms of cerebellar

ataxia. His progressive symptoms were mostly experienced as deficits in the movement modalities. His later symptoms were as follows: four limb dysmetria, wide based ataxic gate, diplopia in right lateral gaze and spinal cord herniation (Boncoraglio et. al., 2011).

As is indicative of a wide range of movement dysfunction, an MRI scan showed hypointensities which focused around the cerebellum and the brainstem.

Case Study 6

This next patient was a 51 year old male. While he did have the classical symptoms of visual deficits and motor disturbances, he also initially presented with a variety of cognitive impairments (Yavagal et. al., 2010). These impairments included increasing confusion and deteriorating mental capacity, as well as difficulties handling multiple tasks at work. In addition to these symptoms, he also experienced hearing loss, a difficulty with balance and anosmia which was present for several months.

The patient's progressive symptoms included on and off aphasia symptoms, dizziness, speech difficulties, apraxia, mild ataxia, and over reactive reflex responses.

EEG results showed left temporal slowing, and MRI imaging showed cerebellar atrophy and T2 hypointensity along the surface of the brain.

Case Study 7

As a 68 year old male, patient 7 was one of the older patients in the current review. Interestingly, this patient suffered from bouts of hallucinations (both auditory and visual) as well as delusions of persecution (Imai et. al., 2011). He was originally diagnosed with a chronic subdural hematoma, which had arisen after the patient had hit his head. He was later cured of this initial hematoma.

Even though his initial symptoms were of a different nature than the rest of the reviewed cases, his progressive symptoms remained fairly mild in comparison to the other studies. Patient 7 experienced worsening gate difficulties as well as hearing loss.

Axial T2-weighted MRI data revealed abnormal atrophy in the temporal cortex, as well as the cerebral cortex and the cerebellum. Single photon emission computed tomography demonstrated a mild low perfusion located in the left frontal cortex as well as the left temporal cortex, with preserved perfusion in other cerebral cortices. Structural MRI scans revealed a rim of hypointensity found around the brain stem, cerebral cortex and cerebellum, which is consistent with previous studies.

Case Study 8

In contrast to the previously mentioned study, Patient 8 was one of the youngest SS patients found in the literature. Patient 8, male, initially presented with symptoms at the age of 19. As this was a three day study, only initial symptoms were documented. The patient was referred due to the sudden appearance of headaches and vomiting which lasted for three days (Wang & Gong, 2009). Upon examination, his neurological status did not indicate any abnormalities besides a moderately stiff neck.

MRI revealed many small blood vessel abnormalities in the patient's brain. These vessels were enlarged and irregular, with exceedingly thin walls. T2-weighted and susceptibility weighted images demonstrated the typical hypointensity around surface of the brain. As previously noted, this hypointensity is consistent with the depositions of hemosiderin found in a positive diagnosis of superficial siderosis.

Case Study 9

Representing one of the three female patients in this study, patient 9 (age= 65) initially presented with gait disturbances and deficits of balance which developed over a period of 4 weeks. After around 6 weeks since the start of the symptoms, the patient began to experience a mild hearing impairment (Uttner, 2009).

Upon examination of the imaging data (obtained with T2- and T2*-weighted gradient echo brain MRI) the patient demonstrated a definite hypointensity due to hemosiderin deposits surrounding the cerebellum. Additionally, these deposits were also located around the midbrain region of the brainstem.

Case Study 10

Patient 10, a 37 year old male, first began to develop gate difficulties (ataxia) in his early thirties, as well as slight hearing loss, spastic paresis, motor-speech deficits, and incontinence. However, these symptoms were preceded by trauma, which occurred when the patient suffered a severe odontoid fracture (Kondziella & Zetterberg, 2008). This fracture led to right-sided hemiparesis, the symptoms of which resolved a few months after the incidence. While this left him with a mild weakness in his right hand, his development until his 30's was otherwise unremarkable.

The MRI scan of the patient's brain and spinal cord demonstrated mild demyelination of the pons and hemosiderin deposits around the cerebellum, brain stem and spinal cord. No obvious source of the bleeding could be found which would allow a surgical procedure to minimize the bleeding. The patient's neuropsychological profile was unremarkable for deficits.

Case Study 11

Case study 11, the final case study of this review, is a 57 year old male. His symptoms first became evident at the age of 54, where he presented with the typical initial symptoms of progressively deteriorating gate steadiness as well as hearing loss (Renard, 2008). Upon examination, the patient demonstrated ataxia and dysarthria as well as sensorineural hearing deficits.

Imaging results demonstrated the classical atrophy present in the cerebellum. This atrophy was found in addition to hypointensity located along the cerebral convexities, fissures, the brain stem, regions of the cerebellum and the eight cranial nerves. The hypointensity was located using T2- as well as gradient-echo T2-weighted MRI.

Overview of Major Symptoms and Imaging Results

Table 3 presents the case studies, along with the major symptom categories and subsequent imaging findings.

Table 3: Symptoms and Major Imaging Results

Case Study	Age	Gender	Symptom Categories	Imaging Results
1	56	Female	Cognitive, Motor, Sensory	Hypointensity around spinal cord
2	48	Male	Motor	Cerebellum atrophy
3	53	Female	Motor, Sensory	Hyperintensity on T1 around the pial surface Hypointensity on T2 around the cerebellum, brainstem, spine and cerebral hemispheres
4	49	Male	Cognitive, Motor, Sensory	Hemosiderin deposits on midbrain, mesencephalon, tegmentum, cingulate sulcus
5	69	Male	Motor	Hypointensity around cerebellum and brainstem

6	51	Male	Cognitive, motor, sensory, speech	Slowing of the left temporal lobe Cerebellar atrophy T2 hypointensity on the brain surface
7	68	Male	Cognitive, motor, sensory,	Temporal and cerebellar atrophy
8	19	Male	Headache and vomiting	Brain surface hypointensity
9	65	Woman	Motor, sensory, cognitive, speech	Hypointensity on cerebellum an midbrain of brainstem
10	37	Male	Motor, Sensory	Demyelination of pons, Hypointensity around basal cerebral sulci, the cerebellum, brain stem and spinal cord
11	57	Male	Motor, Sensory	Cerebellar atrophy Hypointensities found in the cerebral convexities, sylvian and interhemispheric fissures, brain stem, cerebellar folia and the eight cranial nerves

Discussion

Through the previously described 11 case studies, it is obvious that there are certain regions severely affected by superficial siderosis. The most commonly affected is the cerebellum, with 8 of the 11 cases suffering from cerebellar damage. Additionally, hemosiderin deposits occur on the cerebral surface (n=3) and brainstem (n=7).

Motor symptoms were the one of the largest categories of symptoms experienced. There is a strong relationship between cerebellar damage and motor disturbances. 8 of the 10 patients that suffered movement disorders exhibited imaging results indicative of cerebellar damage. Only 1 patient presented with motor deficits and no cerebellar damage. Additionally, only 1 patient was negative for motor symptoms.

Sensory symptoms were another frequently experienced symptom category, with 8 patients suffering from forms of sensory deficits. Of the patients presenting with sensory deficits, 5 of the 8 demonstrated spinal and/or brainstem dysfunction. 2 patients presented with speech deficits, both which also demonstrated abnormal cerebellar imaging results, and 5 patients suffered from cognitive deficits.

The study of SS through the use of functional Magnetic Resonance Imaging would provide a novel technique with which to gain insights into this enigmatic disorder. Functional Magnetic Resonance Imaging is quickly becoming crucial in both the clinical and research aspect of neurological disorders. In past studies, fMRI has helped researchers to more effectively measure the plasticity of the brain after neural insult, such as in the case of Multiple Sclerosis (Weiller et. al., 2006). As proposed by Weiller et al., 2006, the use of fMRI would greatly benefit the study of neurological disorders. The researchers state that fMRI could help further our understanding of the principles of reaction mechanisms and repair in the brain following injury. Through the use of fMRI, researchers and clinicians gain the ability to more delicately assess the damage done by a disorder.

In both stroke and MS, fMRI has shown the specific brain reorganization patterns present in patients as their disease progresses. While stroke is quite unlike SS (one results from an isolated event, whereas the latter is a gradual onset), MS shares a similar pattern of onset. Previous research has shown that fMRI can accurately indicate the level of brain reorganization present in MS patients. Furthermore, detailed knowledge of these reorganization patterns has helped aid clinicians in their selection of both medication and therapeutic techniques. For example, it is a common practice to utilize physiotherapy and CIMT to treat both stroke and MS. These therapeutic methods have been shown to trigger cortical rearrangement. This

rearrangement has has been correlated with improvement of symptoms (Traversa et. al., 1997). Here, knowledge of the inner workings of the neurologically impaired brain can aid in validation of certain therapeutic techniques.

Similarly, a positive presentation of SS was misdiagnosed as a case of Amyotrophic Lateral Sclerosis (ALS). In ALS, fMRI studies have shown that upon the degradation of motor neurons, the brain recruits other regions that are more active during various other motor tasks to assist in the execution of movement (Driver-Dunckley, 2010). Additionally, in patients with ALS, there is a marked increase in the task-related BOLD signal, which is observed in the premotor area. This increase in BOLD in the premotor area was also noted along with an increase in the firing rate as well as the recruitment of premotor neurons (Konrad et. al., 2002). The use of fMRI in the study of SS would help to demonstrate the possible presence of similar patterns of rearrangement due to the neural insult from the injury, which could help guide research in an even more specific direction.

Conclusion

While there is no known definitive treatment for SS to date, by comparing fMRI data of this disorder to other well-studied disorders, it would be possible to deduce what form of therapy would best fit this disorder. The greater the similarity in brain reorganization as the disorders progress, the greater the chance that similar treatments would be effective for both disorders.

However, one of the crucial benefits of fMRI (as is with structural MRI) as a method of studying SS is its non-invasive nature. Previously, as is the case with Alzheimer's and other dementing disorders, a definitive diagnosis could not be made until a post-mortem autopsy was conducted. Now, through the use of MRI doctors have the ability to diagnose this disorder early.

A rapid diagnosis can assist treatment and rehabilitation in a more direct way, which can better help the patient towards a more fulfilling life.

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ACADEMIC VITAE OF CAITLIN OGRAM

EDUCATION

Psychology; Science, 2012 – The Pennsylvania State University, University Park, PA

RESEARCH EXPERIENCE

Research Assistant

Laboratory for Traumatic Brain Injury **October 2010- present**

Faculty Supervisor: Dr. Frank Hillary

- Researched the effects of age on functional outcome after traumatic brain injury using the Pennsylvania Trauma Systems Database
- Developed expertise in SPSS and SPM 8 software

Research Assistant

PSU Sports Concussion Neuropsychology Program **December 2010 – present**

Faculty Supervisor: Dr. Peter Arnett

- Received training on administration of the PSU Concussion neuropsychological battery
- Tests administered included HVLT, BVMT, RBMT, Digit Span, Stroop word/color inhibition, and imPACT computerized testing
- Have administrated the battery 20 times in the past year to athletes at baseline and post-concussion

Independent Project

Penn State Forensic Science Department **January 2010-April 2010**

Faculty Supervisor: Dr. Robert Shaler

- Assisted professor in the collection and analysis of data pertaining to the effects of extreme weather conditions on latent fingerprints

HONORS THESIS

Ogram, C.M., Hillary, F.G., (2012) Superficial Siderosis of the Central Nervous System: A Proposal for the Use of Functional Magnetic Resonance Imaging in Clinical Research

CONFERENCE PRESENTATIONS

Ogram, C.M., Ramanathan, D.M., & Hillary, F.G. (2011). Functional Independence in the Elderly Following Traumatic Brain Injury. Poster presented at the Annual Psi Chi Undergraduate Research Conference, University Park, PA **April 2010**

Ogram, C.M., Ramanathan, D.M., & Hillary, F.G. (2011). Functional Independence in the Elderly Following Traumatic Brain Injury. Poster presented at the Penn State Undergraduate Research Exposition, University Park, PA **April 2010**

Ogram, C.M., Ramanathan, D.M., & Hillary, F.G. (2012). Age Disparities in Functional Outcome Following TBI. Presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, Quebec, Canada **February 2012**

TEACHING EXPERIENCE

Undergraduate Teaching Assistant: Duties included holding weekly office hours for students, as well as setting up and leading review sessions for the exams

Psych 260- Neurological Basis of Behavior **January 2011-May 2011**

Peer Tutor: Duties included organizing weekly meetings with students to reinforce concepts taught during that week's lectures

Biology 110- Concepts in Biodiversity **October 2010- December 2010**

Biology 141- Anatomy and Physiology **January 2011-May 2011**

Psychology 100 **August 2011-present**

ACADEMIC SERVICE

Member of the Paterno Fellows Advisory Board **October 2008- present**

Co-founder of Psych Squad, a Psychology club **April 2009**

Note taker for the Office for Disability Services **September 2009-December 2009**

Volunteer for the American Heart and Stroke Association **February 2012**

AWARDS

Schreyer Honors College Scholar **Spring 2009- Present**

Paterno Liberal Arts Undergraduate Fellow **Spring 2009- Present**

Gundaker Rotary Undergraduate Grant **Fall 2011**

Presidential Freshman Award **Fall 2008**

Minerva Brown Liberal Arts Scholarship **Fall 2007**

East Caln Town Watch Crime, Law and Justice Scholarship **Spring 2008**

Joe Martin Bank of America Scholarship **Spring 2008**

Liberal Arts Scholarship **Spring 2009, 2010, 2011**

Dean's List **Every semester**

Third place- the Penn State Undergraduate Research Exposition **April 2010**