Visual evoked response and visual reaction time in chronic arachnoiditis

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VISUAL EVOKED RESPONSE AND VISUAL REACTION TIME IN CHRONIC ARACHNOIDITIS

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requirements for admission to the degree of
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This work is dedicated to Tim Owen (1968-1996)

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Chronic arachnoiditis is an inflammatory condition affecting the pia-arachnoid membranes of the brain and spinal cord. It may result from infection or trauma but more recently has been diagnosed secondary to contrast myelography. In such chemically-induced cases, an acute meningeal foreign body reaction develops within hours of the procedure, sometimes involving vision. Chronic inflammation may also develop years later quite independently of the initial reaction. Little is known about the potential visual effects of chronic arachnoiditis, but as chemicals injected intrathecally can remain in close proximity to the visual pathway, a low grade inflammatory process affecting vision could occur.

To investigate this hypothesis 11 chronic arachnoiditis subjects were examined with a battery of tests known to be sensitive to visual pathway involvement. Testing included routine examination of visual function, recording of visual evoked cortical potentials and measurement of simple visual reaction time.

Results showed that patients with arachnoiditis confined to the lumbar spine were visually normal. Patients with a more widespread arachnoiditis showed definite visual involvement characterised by an increase in latency and reduction in amplitude of the visual evoked cortical potential. Reported symptoms included pain or burning in and around the eyes, intermittent blurring and occasional loss of vision. Clinical findings included reduced acuity in the symptomatic eye, reduced contrast sensitivity to large spatial frequencies, an afferent pupil defect and optic nerve head pallor. Changes in the visual evoked cortical potential were correlated to the experience of symptoms but not to the duration of disease. There was an increase in latency of the fastest visual reaction time and a greater increase in the average visual reaction time which suggests a cognitive impairment in addition to the sensory-motor loss.

The visual findings suggest a deficit of the magnocellular pathway not unlike that found in multiple sclerosis and are consistent with the suspected pathological process of demyelination. The wider implication of these findings is the possibility of other central nervous system effects and the obvious need to move away from contrast myelography towards less invasive techniques.

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ABSTRACT

Arachnoiditis is an inflammatory disease process affecting the pia-arachnoid membranes of the brain and spinal cord, that may result from infection or trauma, but more recently has been diagnosed secondary to myelography.[1] This chemically induced form usually occurs as an acute meningeal, foreign body reaction that develops within hours of the chemical exposure and lasts a few days.[2] A chronic adhesive form of arachnoiditis, however, involving the wider central nervous system,[3] can develop months to years later quite independent of the acute reaction.[4] While visual effects of acute arachnoiditis are well documented and parallel those of general meningitis, little is known of any chronic visual effects.

Chronic adhesive arachnoiditis is characterised by progressive inflammation of a immunological origin[2] that leads to atrophy of nerves and related neurological deficits.[5] Experimental evidence suggests that the process leading to atrophy is demyelination.[6] As chemicals injected intrathecally can remain in close proximity to the visual pathway an investigation was undertaken to examine the possibility that the visual pathway can be adversely affected. It is expected that patients with a more rostral arachnoiditis would be more likely to exhibit visual defects and that any effects found would parallel those of other demyelinating disease such as multiple sclerosis.

Eleven chronic arachnoiditis patients were examined with a battery of tests known to be sensitive to visual pathway involvement in multiple sclerosis. Testing included routine examination of visual function, recording of visual evoked cortical potentials and measurement of simple visual reaction time. Results showed that patients with arachnoiditis confined to the lumbar spine were visually normal, whereas patients with a more widespread arachnoiditis

showed visual involvement characterised by an increase in latency and reduction in amplitude of the visual evoked cortical potential. Reported symptoms included pain or burning in and around the eyes, intermittent blurring and occasional blacking out of vision. Clinical findings included reduced acuity in the symptomatic eye and reduced contrast sensitivity to large spatial frequencies. Changes in the visual evoked cortical potential were correlated to the experience of symptoms but not to the duration of disease. There was also an increase in latency of the fastest visual reaction time and an even greater increase in the average visual reaction time which suggests a cognitive impairment in addition to the sensory-motor loss.

All visual findings suggest a deficit of the magnocellular pathway not unlike that found in multiple sclerosis. Characteristics of the visual evoked cortical potential support the theory that the underlying process is demyelination which could be due to direct exposure to the contrast agent but is more likely secondary to the ensuing arachnoidal inflammation. Regardless of the process, the wider implication of this visual involvement is the possibility of other central nervous system effects.

Further work is required to establish the exact aetiology of the visual loss and to understand what happens to vision over time. Nevertheless, this study provides sufficient evidence to add visual involvement to the list of neurological deficits associated with chronic adhesive arachnoiditis and may add some further pressure to move away from contrast myelography to less invasive techniques.

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TABLE OF CONTENTS

CHAPTER 2 MATERIALS & METHODS

CHAPTER 3 RESULTS

ABBREVIATIONS USED

AIDS	acquired immune deficiency syndrome
ANOVA	analysis of variance
CNS	central nervous system
CS	contrast sensitivity
CSF	cerebral spinal fluid
CT	computerized tomography
Cz	vertex
Diffuse	arachnoiditis diffuse to the central nervous system
EEG	electroencephalograph
Focal	arachnoiditis confined to the spine
FVRT	fastest visual reaction time
HIV	human immunodeficiency virus
LCVA	low contrast visual acuity
LED	light emitting diode
MRI	magnetic resonance imagery
MS	multiple sclerosis
ms	milliseconds
N1	first negative peak
N2	second negative peak
NS	not significant
Oz	inion
P1	main positive peak
PERG	pattern electroretinogram
PVECP	pattern visual evoked cortical potential
SD	standard deviation
μV	microvolts
VA	visual acuity
VECP	visual evoked cortical potential
VRT	average visual reaction time

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

1.1 ARACHNOIDITIS

1.1.1 Definition

Arachnoiditis is a progressive, non specific inflammatory disorder affecting the arachnoid tissue of the spinal cord and brain. Either the spinal cord and/or the brain may be involved and it may be associated with meningitis.[3-5] Table 1.1 lists the many synonyms for this rare disorder.[4]

TABLE 1.1 ***Synonyms for arachnoiditis***[4]

adhesive arachnoiditis	optochiasmatic arachnoiditis
arachnitis	postmyelographic arachnoiditis
arachnoiditis ossificans	serous circumscribed meningitis
cerebral arachnoiditis	spinal arachnoiditis
chronic adhesive arachnoiditis	spinal ossifying arachnoiditis

Arachnoiditis may result from infection, including syphilis and tuberculosis, from trauma, including subarachnoid hemorrhage, spinal surgery, lumbar puncture and spinal anesthesia, and also as a foreign body reaction to a drug injected into the subarachnoid space.[7-10] First described by Krause in 1907, it was commonly of an infectious nature but with advances in medicine, trauma and intrathecal chemicals are now the more common aetiologies.[11,12]

Diagnosis is usually by myelography[11] but unfortunately myelography itself can cause arachnoiditis, as it involves the injection of a contrast agent into the subarachnoid space.[5]

1.1.2 Brain, Spinal Cord and Optic Nerves Meninges

To better understand the relationship between a chemical injected intrathecally and the possible development of arachnoiditis, it is appropriate to first review the structure of the meninges and the pathophysiology of arachnoiditis.

The human brain and spinal cord are surrounded by three layers of protective meninges, the dura mater, the arachnoid and the pia mater. The arachnoid and pia mater are separated by the subarachnoid space and are often referred to as the leptomeninges.[13]

Cerebral dura mater is composed of two layers, the meningeal layer that covers the brain and the periosteal layer that is firmly attached to the calvaria. Inside the skull the two layers are closely attached to each other except in certain areas where they are separated by the dural sinuses. Below the foramen magnum, in the spinal canal, these two layers of the dura become separated to enclose the epidural space.[14]

The arachnoid mater is a delicate, transparent membrane surrounding the brain and spinal cord. It is firmly attached to the dura and loosely attached to the cerebral matter via the pia. On the upper surface of the cerebrum it is thin and transparent and passes over the convolutions of the brain without dipping down into the various sulci. At the base of the brain the arachnoid tissue is much thicker where it covers the anterior lobes, the two middle lobes, the pons and the cerebellum. At all points it is separated from the pia mater by the subarachnoid space which contains cerebrospinal fluid (CSF). The subarachnoid and subdural spaces of the cranium and spinal cord are directly continuous and represent the spaces through which injected agents can move as shown in Figure 1.1. There are two large subarachnoid spaces, one anteriorly and the other between the cerebellum and the

medulla oblongata. At the very base the arachnoid tissue gives rise to the sheaths of the cranial nerves as they exit the brain to the spinal cord.[14,15]

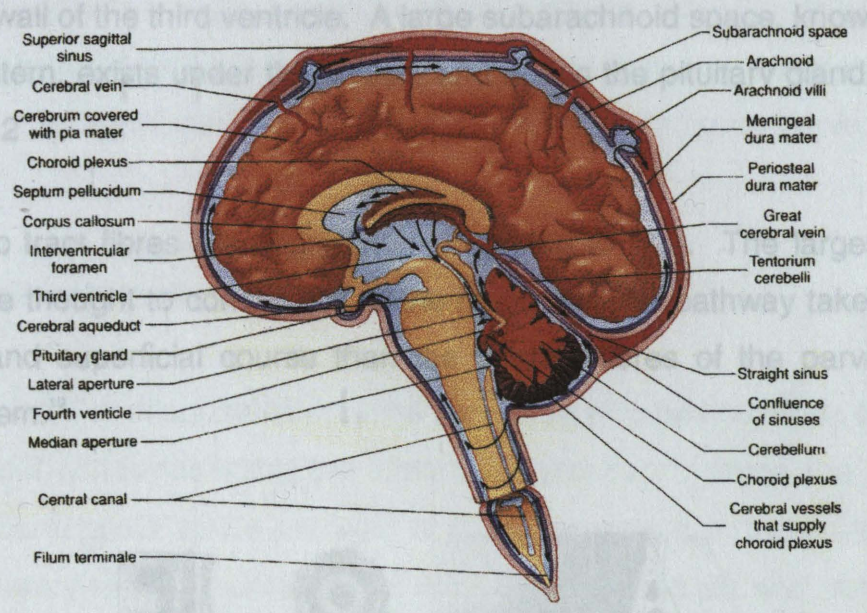


FIGURE 1.1 ***Subarachnoid spaces and CSF pathway through which an intrathecally injected substance can potentially travel.***

(From Spence AP and Mason EB: Human Anatomy and Physiology, St. Paul, West Publishing Company, 1992)

The meninges of the brain are also intimately related with the visual pathway as suggested by the visual symptoms that can occur in meningitis.[16,17] From the lamina cribrosa to the canal, the optic nerve is surrounded by the inner layer of pia mater, the arachnoid, and the tough outer layer of dura. The pial septae originate posterior to the lamina cribrosa and gradually take over and enclose all neural tissue. The arachnoid mater also originates at the lamina cribrosa and the space between the pia and the arachnoid is continuous posteriorly with the subarachnoid spaces of the brain described earlier. The arachnoid is composed of collagenous tissue, small amounts of elastic tissue and meningothelial cells.[18]

The optic nerve exits the optic canal of the sphenoid bone through a fold of dura at the posterior end of the canal and runs posterior-medial to the chiasm to give rise to the optic tracts. The chiasm sits 10-12 millimetres above the posterior wall of the sella with its posterior edge forming the anterior wall of the third ventricle. A large subarachnoid space, known as the basal cistern, exists under the chiasm and above the pituitary gland.[3,18] See Figure 1.2

The optic tract fibres are segregated according to size. The larger axons, which are thought to correspond to the magnocellular pathway take a more ventral and superficial course than the smaller fibres of the parvocellular sub-system.[19]

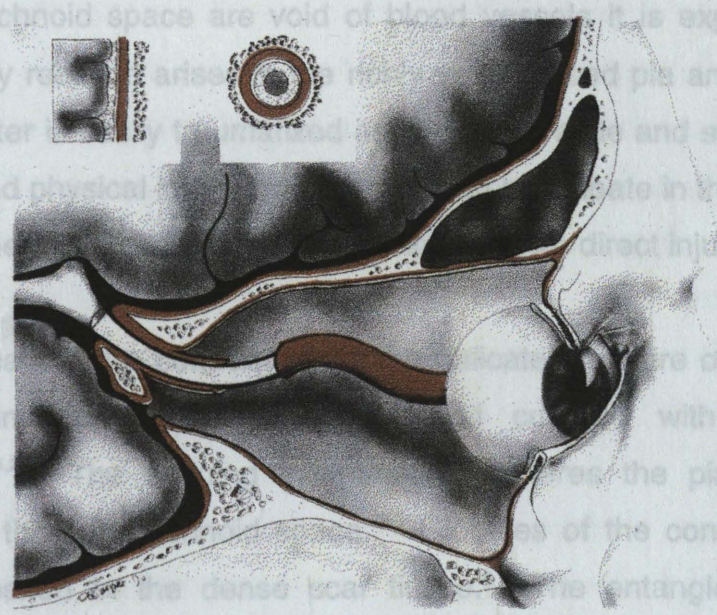


FIGURE 1.2 ***Schematic view of subarachnoid space showing the continuous nature of the subarachnoid space with the optic pathway.*** Inset shows the meninges of brain tissue and optic nerve in cross section.
(From Casper DS, Chi TL and Trokel SL: Orbital Disease Imaging and Analysis, New York, Thieme Medical Publishers Inc, 1993)

An intrathecally injected agent could assume the same pathway as the CSF flowing through the subarachnoid space and potentially pooling in the basal cisterns. Because of the close proximity of the basal cisterns to the optic chiasm and the continuous nature of this space with the subarachnoid space of the optic nerves, there is potential for accumulation and exposure of the contrast agent to a large area of the visual pathway. With the delicate nature of the arachnoid tissue, it is not unreasonable to speculate that accumulation of a contrast agent could cause ongoing irritation to the optic nerve.

1.1.3 Pathophysiology

Arachnoiditis is characterized by the formation of granulomatous tissue and nerve root adhesions within the leptomeningeal sac.[20] Since the arachnoid and subarachnoid space are void of blood vessels it is expected that the inflammatory reaction arises in the richly vascularised pia and dura mater.[11] The pia mater is easily traumatized as it is very fragile and sensitive to both chemical and physical injury[8] and the dura can participate in the production of dura-leptomeningeal adhesion even without its own direct injury.[11]

Upon application of a contrast agent the delicate structure of the arachnoid tissue is invaded by macrophages and covered with a fibrin like substance.[11,21] The ensuing inflammation adheres the pia to the dura, obliterating the subarachnoid space.[22] Globules of the contrast agent are often enmeshed in the dense scar tissue.[8] The entangled nerve roots hypovasculate and become progressively atrophic.[23]

The CSF is thought to wash away the phagocytes and enzymes that usually help reduce inflammation[8,24] and there may also be a enzyme defect involved[25] which could explain why arachnoiditis occurs in some people but not in others.

The process of enmeshment is insidious and despite significant radiological signs, symptoms may not occur for many years. When the arachnoiditis is associated with an anatomical deformity, which is usually of the spine, the symptoms originate at that level of the spine that is involved.[8]

1.1.4 Diagnosis

The diagnosis of arachnoiditis is based on clinical history, examination including CSF analysis and radiography, and on surgical findings.

Arachnoiditis symptoms are unusual and are often dismissed as neurotic or functional or confused with sciatic and rheumatic syndromes.[8] Symptoms can also be inconsistent but the clinical syndrome often includes burning pain in the back and legs, impotence in males, limitation of spinal movement, weakness in the legs and a need for regular analgesia.[24,26] Pain is the significant feature, with one study reporting 96% of patients with lower back pain and 98% with leg pain.[5] Headache, bladder and bowel dysfunction are also common.[27] No other disease causes this burning sensation which is also reported in the insteps, inner aspects of the knees and in the lumbo-sacroiliac area.[8] Patients however often go undiagnosed for years until a diagnosis is eventually made by exclusion.[8]

Symptoms often contradict signs and some patients are symptom-free despite significant radiological signs.[26,28,29] The interval between the possible aetiological event and diagnosis can vary from weeks to over 30 years.[29] Symptoms fluctuate over the years and the majority of patients continue to drive and walk. However patients are often unable to return to work and the average life span is reduced by 12 years.[5,29]

Typical myelographic findings include restricted CSF flow, irregularities of the subarachnoid space, thickening of nerve roots and spinal cord atrophy.[30,31] If the CSF is totally blocked protein is usually elevated[5,11,29] and immobile droplets of contrast agent are seen throughout the lumbar space.[32] This view may remain for many years[33] however it is also possible to have a normal myelogram that on post-mortem shows arachnoiditis.[11]

Even though myelography is known to cause arachnoiditis, it remains as the gold standard in diagnosis of the disease.[34] This is because less invasive techniques like computerized tomography (CT), unless used with a contrast agent, only show arachnoiditis that is extensively ossified.[30,32,35]

Magnetic resonance imagery (MRI), however, can demonstrate arachnoidal changes sufficient for diagnosis. In fact, the use of a contrast agent does not aid the diagnosis except in the recognition of adherent roots.[36] MRI studies of chemical meningitis have shown that the majority of patients have leptomeningeal involvement and only 12% have dural involvement.[37] Of the arachnoiditis cases 88% are diffuse and the remainder focal.[23] MRI results using T2 weighted images are consistent with contrast CT scans and plain films, and offer the advantage of requiring no contrast agent.[22,38,39] There has also been recent success in imaging arachnoiditis with enhanced MRI using Gd-diethylenetriamine penta-acetic acid.[31] Regardless of these advances, when better intrathecal definition is required, unfortunately contrast myelography provides the best view.[9]

Because arachnoiditis often coexists in patients requiring spinal surgery it is often confirmed at operation.[40] The surgical view shows a yellowish dura adherent to the arachnoid which eventually becomes thickened and opaque. The fibrosis that obliterates the subarachnoid space is seen to strangle the spinal cord and nerve roots.[11,41]

1.1.5 Classification

Arachnoiditis is classified either according to the severity of its radiological appearance[22] (Table 1.2) or by the known stages in the inflammatory process.[42]

TABLE 1.2 *Delmarter[22] classification of arachnoiditis*

Type	Radiological Appearance
I	Central clumping of nerve roots
II	Peripheral adhesion of nerve roots to the theca
III	Complete opacification of the thecal sac

Stage one, or radiculitis, is characterized by minimal fibroblast proliferation with hyperemia and swelling of the nerve roots. Radiculitis is a very common entity that frequently presents following injury, spine surgery or infection, and is unlikely to be of clinical significance.[42]

Stage two, or arachnoiditis, represents progressive fibroblast proliferation and collagen deposition between the nerve roots and the pia arachnoid. The inflammatory swelling subsides but the roots remain adherent to each other and the pia-arachnoid. When the inflammation is focal it may be associated with significant clinical problems. Arachnoiditis is typically located in the lower spine as a result of lower back injury and spinal surgery.[42]

Adhesive arachnoiditis is the end stage of the inflammatory process and is characterized by proliferation of dense collagen deposition which completely encases the nerve roots, depriving them of their blood supply and resulting in atrophy.[42] Adhesive arachnoiditis is the least common form of arachnoiditis but the most serious due to the potential effects on the entire CNS. There is significant disability related to pain and an increased likelihood of progressive neurological impairment.[43]

1.1.6 Prevalence

Since radiculitis and arachnoiditis are often sub-clinical it is not surprising that the prevalence of these two conditions is unknown. It is also difficult to establish the exact incidence of adhesive arachnoiditis but it is now fairly well accepted that the use of contrast agents and operations for discectomy and laminectomy account for the majority of cases that originate in the lumbar region.[24] A MRI study of patients at least one year after surgery showed a 20% prevalence of arachnoiditis, that dropped to 3% when patients who had been injected with oil-based contrast agents were excluded.[23]

Of the 300000 to 400000 patients that undergo back surgery in the US each year, about 25% are made worse or not improved by the surgery. From this group, 11% have adhesive arachnoiditis as the primary disease process producing the incapacitation.[43,44] Lower incidences that have been reported[11] might only be the result of less vigorous methods of diagnosis. It is also unclear as to how many cases progress, as some claim 0-25% progress while others believe paraplegia will always be the end result.[5] For the cases that do progress the majority are related to Myodil® (iophendylate) myelography.[43] (Table 1.3) Since 1940, 450000 Myodil® myelograms have been performed annually[43] with approximately 1% of cases leading to adhesive arachnoiditis.[32,45] Excluding neoplastic arachnoiditis, it can be estimated that over the last fifty years, 500000 US patients developed adhesive arachnoiditis due to myelography and/or surgery.

TABLE 1.3 *Causes of adhesive arachnoiditis*[43]

Cause	Percentage
Myelography with iophendylate	93
Trauma segmental to spine from car accidents	4
Trauma segmented to spine at surgery	1
Foreign body deposition in subarachnoid space - steroids	1
Others	1

1.2 ARACHNOIDITIS SECONDARY TO MYELOGRAPHY

1.2.1 Pathophysiology

When a contrast agent is used intrathecally, patients are at risk of complications, as the installation of any agent into the CSF can cause direct chemical irritation and meningitis.[46] Even the accidental introduction of glove powder into the subarachnoid space has resulted in arachnoiditis.[47]

The volume of contrast agent injected is related to the extent of tissue being examined.[48] Large volumes are used more caudally and more conservative doses used rostrally. The most common arachnoiditis is lumbo-sacral[8] either reflecting the effect of larger doses, a more common site of injection, the site of injury and surgery, or possibly the area in which agents accumulate.[49]

Two proposed mechanisms have been hypothesized, direct meningeal irritation and a delayed-hypersensitivity type reaction. The direct meningeal irritation is thought to reflect acute meningitis and the hypersensitivity reaction may result in the chronic adhesive form of arachnoiditis.[46] There seems to be an association between the occurrence of the hypersensitivity reaction and underlying collagen vascular or rheumatologic disease.[46] As in the peritoneum, there is a tendency of the arachnoid to continue the inflammatory reaction long after the inciting agent has ceased to be active.[15]

The end result is an ischaemic atrophy of locally involved nerve roots. At a microscopic level, experimental evidence has shown myelin degeneration and proliferation of Schwann cells[6] not unlike multiple sclerosis.

1.2.2 Contrast Agents and Adverse Effects

Contrast agents are used in myelography to increase the visibility of the outline of structures within the body by increased absorption of x-rays in

extracellular fluid-filled spaces. Most agents are iodinated organic compounds that have a radiodensity proportional to their iodine content.[50] Myelography was originally performed with air and then oxygen, prior to the development of the first oil based agent, Lipiodol®.[48,51] Other lipid based dyes were used extensively throughout the 1940's and 50's until the introduction of water soluble ionic dyes in the 1960's.[52] The dyes in current use are non-ionic and water soluble.[50] (Table 1.4)

Table 1.4 ***Development of contrast agents***

Year	Contrast Agent	Iodine %	Brands (Manufacturer)	Main Complication
1918	air, oxygen	0		poor view
Oil Based Agents				
1922	iodized oil		Lipiodol®	chronic arachnoiditis
1944-1991	iophendylate	30.5	Myodil® (Glaxo), Pantopaque® (Alcon)	chronic arachnoiditis
Water Based Agents - Ionic				
1931-	methiodal sodium		Kontrast U, Conturex, Abrodil	extremely irritating
1938	thorium dioxide		Thorotrast®	acute & chronic arachnoiditis
1960s	meglumine iothalamate	47.1	Conray	chronic arachnoiditis
1960s	meglumine iocarmate		Bis-Conray, Dimer-X®, Dimeray	chronic arachnoiditis
Water Based Agents - Nonionic				
1973	metrizamide	48.25	Amipaque® (Winthrop)	acute and chronic arachnoiditis
1970s	iohexol	46.4	Omnipaque® (Winthrop)	acute changes
1970s	iopamidol		Isovue, Niopam (Merke)	acute changes

1.2.2.1 Oil Based Agents

The main oil based agents, Myodil® and Pantopaque® had widespread use during the 1940's to the 1980's.[8] Pantopaque® is a mixture of ethyl esters of isomeric iodophenylundeclic acids which contain firmly bound organic iodide[48] and Myodil® is a mixture of stereoisomers of ethyl 10-(4-iodophenyl)undecanoate containing about 30.5% of iodine. Both are very slightly soluble in water and freely soluble in alcohol, chloroform and ether. Acute side effects reported by the manufacturers include headache, backache, neck stiffness, nausea, vomiting, fever and the more serious effect of allergy. An acute aseptic meningitis has been reported to occur in approximately 0.05% of Myodil® cases which is why it is recommended that the agent be removed from the spinal column after the examination.[2,50]

In spite of these recommendations, aspiration of the dye was infrequent and the most commonly reported complication of iophendylate use was this acute arachnoiditis which occasionally progressed to a chronic adhesive form.[2] In the acute cases, symptoms resolved as the contrast agent was reabsorbed.[53] In chronic disease, CSF analysis showed lymphopleocytosis, elevated protein and decreased glucose[46] indicative of an underlying immunological mechanism.[54] Chronic cases may have been due to the contrast agent, the surgery or existing vertebral disease.[29] Cases that developed in the thoracic and cervical areas, away from the original injury, implicate contrast agents[29] but it is also known that people have more thecal scarring following Myodil® and surgery than just Myodil® alone.[52] It fact, it seems that chronic arachnoiditis is unlikely to develop following myelography alone[55,56] but instead only in the presence of existing inflammation. It has also been shown that a blood-Pantopaque® mixture is more noxious than Pantopaque® alone[57-59] which becomes significant when an epidural or intrathecal injection has been traumatic.

The arachnoidal reaction is usually mild in the cervical spine and most severe in the caudal sac.[60] It can also develop in the brain following cervical injection[61] or from a lumbar injection that has been manipulated in to the ventricular system.[49]

Pantopaque® was introduced in 1944 and banned in Sweden only four years later and in Britain by 1990. A class action suit is pending in Britain of 25000 people. In 1986, Kodak, the company that manufactured Pantopaque®, voluntarily stopped distributing the drug in the USA and the protests of sufferers has resulted in a proposed bill to ban all forms of myelography.[62] The Australian Adverse Drug Reactions Bulletin noted the relationship between the retention of Myodil® and adhesive arachnoiditis in February 1975. It was subsequently raised in parliament in 1994 and is soon to be an issue of the Federal Courts.[63]

1.2.2.2 Water Soluble Ionics

The first water soluble agent, methiodal sodium (sodium salts), irritated the spinal cord and nerve roots to the extent that spinal anesthesia was necessary to introduce the dye, and spinal anesthesia is not devoid of its own complications. Nerve root irritation was found in 28% of cases and manifested within two to three hours after the examination as the anesthetic was wearing off.[64] The irritation was due to an increase in the osmolarity of the CSF, particularly in the caudal sac, which became the site of subsequent arachnoiditis development.[65] Skalpe reported a 29% incidence of adhesive arachnoiditis from water soluble myelography alone which increased to 48% if the patient had both myelography and surgery.[66]

Thorium dioxide (Thorotrast) is a radioactive contrast agent that was used during the 1930's and 40's. It also caused acute arachnoiditis but was

eventually abandoned following reports of secondary radiation and malignant lesions.[11] A case of adhesive arachnoiditis developing thirty years after Thorotrast myelography has been reported.[41]

Conray (meglumine iothalamate) has been shown to cause thecal scarring in 50% of cases following myelography and in 68% of cases following myelography and surgery, which is almost comparable to Myodil®.[52] Dimer X has similar radiological findings[52] but how these translate into clinical symptoms has not been reported.

1.2.2.3 Water Soluble Nonionics

Metrizamide (Amipaque®) is a nonionic water soluble agent with low toxicity[46] and only half the osmolality of the older dyes.[67] It does not cross the blood brain barrier[67] and because it is completely reabsorbed from the subarachnoid space, chronic arachnoiditis was originally thought to be unlikely.[68] Patients are more likely to experience the acute side effects of headaches, nausea and vomiting, particularly when dye injected into the lumbar spine reaches the cervical area.[67] Fever or slight meningeal signs have been reported following 4-13% of metrizamide myelographies[69] as well as transient visual disturbances and blindness.[70,71]

A chronic case of arachnoiditis was reported in 1980 that involved aseptic meningitis, arachnoiditis, communicating hydrocephalus and Guillain-Barre syndrome. An acute chemical arachnoiditis was followed by a suspected immunologically mediated and more diffuse arachnoiditis.[72]

Later studies showed that in vitro, metrizamide increases the protein and collagen production of fibrocyte cells[73] and in fact kills arachnoid tissue culture.[5] At higher concentrations it has been shown to produce chronic

arachnoiditis in monkeys.[11] Fortunately, if chronic arachnoiditis does develop, it is far less cellular compared to that caused by retained iophendylate.[74]

Other water soluble ionic dyes, iohexol (Omnipaque®) and iopamidol (Isovue) has also been shown to cause an acute reaction but few chronic side effects have been reported.[148] Iohexol has fewer inflammatory side effects because it is isomolaric and can be easily reabsorbed by the CSF[51] but other reported complications include death following subarachnoid hemorrhage.[75]

In spite of these developments towards less toxic agents the situation is still less than satisfactory. In some countries cost restraints have hindered the widespread use of non-ionic agents [76] but it seems that even for those who do use non-ionic agents there is still some risk of developing chronic arachnoiditis.[5]

1.2.3 Treatment

There is no known cure for adhesive arachnoiditis. For the majority of patients adhesive arachnoiditis is a disabling disease causing intractable pain and neurological deficits. As the disease progresses some symptoms may increase and become permanent and few people with this disorder are able to continue working. The goal of treatment therefore is to return the patient to a functional role in society.[1]

The initial treatment for arachnoiditis caused by iophendylate myelography is the removal of the contrast agent from the subarachnoid space.[8] Iophendylate is absorbed slowly at 1 mL per year and although there is no conclusive evidence that reactions to iophendylate are dose dependent, its

removal serves as the best preventative measure. A US Appeal Court ruling in 1971 judged a physician negligent for the non-removal of iophendylate.[77] Preventative measures at the time of myelography include the avoidance of unnecessary introduction of the contrast medium into the cranium by timely extension of the neck and an upright recovery position of the patient.[61]

For milder cases conservative therapy such as pain management, physiotherapy, exercises and stretching are generally recommended.[1,8,43] There is however some doubt over aggressive therapy as activity worsens symptoms.[5] As patients find no real success with traditional therapies some turn to alternative remedies such as biofeedback, meditation and self enhancement programs.[43]

The most common surgical treatment involves conventional decompressive laminectomy. The dura is unroofed and opened to expose the spinal cord. The nerve roots are separated and the fibrous, white collagenous material is teased out without damaging the nerves.[51] Such surgery is more often successful when the arachnoiditis is focal.[78,79] After surgery, adhesions can reform but at least some improvement is gained in up to 50% of cases.[801] Unfortunately improvement is short term with only 15% of cases continuing to experience the benefits of the surgery at two years.[61,11]

An alternative surgical treatment involves lysis of the arachnoidal constriction[32] and antifibrotics to prevent scar tissue reforming.[11] Again short term improvement generally occurs but eventually symptoms return with increased scarring.[5,11,32,61,81]

Controversy surrounds the use of Depo-Medrol, an intrathecal hydrocortisone, used initially to treat back syndromes and with some success in treating multiple sclerosis. Many significant side effects have been recorded including the development of meningitis and severe

arachnoiditis to the point that a number of hospitals banned the drug during 1976-1983.[26,82] In experimental models, Depo-Medrol reduces the chronic meningeal reaction but in clinical practice injections are painful and result in increased inflammation.[11,61] Steroids at high doses have been shown to cause immediate demyelination of central and peripheral nerves in animals.[83] This dose relationship may explain the adverse effects of steroids reported in some studies but not in others.[32] Steroids administered orally are beneficial in acute reactions to prevent arachnoiditis but are of little use in chronic disease.[60,61,84]

Numerous other pharmacological agents such as anti-inflammatories and antineuralgic drugs have also been tried, including phenytoin, carbamazepine, clonazepam, baclofen, thiamine, amitriptyline and haloperidol.[32] Some patients might benefit from d-penicillamine therapy.[85]

Injection of local anesthetic into the lower back gives short term relief[11] but injection into the epidural and subarachnoid spaces is potentially dangerous due to the unpredictable anatomical anomalies of these patients.[86]

Radiotherapy may inhibit adhesion formation but radiation is also known to cause inflammation and fibrosis.[11]

Implantable devices such as dorsal column stimulators, transcutaneous electrical nerve stimulators, deep brain stimulation, and implanted pumps for intrathecal morphine administration provide some relief[87] but require high maintenance[32] and are relatively expensive.[88]

There may be some hope with urokinase, which has been commonly used in treating aneurysmal subarachnoid hemorrhage and intracerebral hematoma. It has recently been demonstrated to prevent the formation of leptomeningeal adhesions in rats.[89] Likewise, Poloxamer 407 has also been

used successfully in rabbits, reducing the adhesion formation following laminectomy and surgical meningeal injury by 50%.[80]

Finally, the social aspect in treating this distressing iatrogenic disease is in developing public recognition so that help and understanding can be given to these sometimes sad and lonely sufferers.[8]

1.3 EFFECTS ON THE VISUAL SYSTEM

Although arachnoiditis is now more commonly associated with myelography and spinal surgery, there are a number of other more classic causes that have well described effects on the visual pathway.

1.3.1 Arachnoiditis Focal to the Optic Chiasm

Optochiasmatic arachnoiditis is defined as a localized inflammatory process at the base of the brain sufficient to affect both optic nerves.[90] It was originally related to tumours of the pituitary that pressed upwards onto the optic chiasm but later it was realised to be from a number of causes including meningitis and trauma. Optochiasmatic arachnoiditis is characterized by thickening of the arachnoid, development of adhesions and occasionally cysts within the subarachnoid space, causing atrophy of visual fibres and visual loss. Clinically the patient presents with visual deterioration of one or both eyes[90-92] secondary to either compression or direct invasion of the optic nerve.[15] The visual loss may be episodic with exacerbations separated by many years[93] that vary from mild to complete blindness. Headaches generally precede visual symptoms. There is a lack of achromatopsia and visual field losses show no set pattern or changes although an absolute central scotoma is common. There may be hyperemia or pallor of the disc and occasionally a sixth or third nerve palsy.[15]

Craniotomy shows thickening of the arachnoid and adhesions in the region of the optic nerves and chiasm. On autopsy the optic nerve shows demyelination. The meninges around the chiasm are thickened and collagenized and contained many lymphocytes, red blood cells and macrophages. Optochiasmatic arachnoiditis is probably a localized form of arachnoiditis similar to that found in the spine that causes vision loss through strangulation of the optic nerve.[94,95] The question as to whether optochiasmatic arachnoiditis is a specific entity or part of systemic disease remains unresolved[94] however optochiasmatic adhesive arachnoiditis with sudden onset of visual loss has also been reported in brothers.[96]

Optochiasmatic arachnoiditis can also develop secondary to tuberculosis infection of the meninges. An enlarged intracranial tuberculoma can compress the anterior optic pathway causing progressive visual loss. Typical symptoms include headache, nausea, vomiting and an elevated CSF white cell count. Visual loss and pupil abnormalities occur with a normal fundus.[97]

Arachnoiditis has also been reported following muslin wrapping of intracranial aneurysms.[98,99] Wrapping of aneurysms to prevent re-bleeding has been used for many years and often involves vessels in close proximity to the optic nerves and chiasm. The first such case was reported in 1879 where a patient developed a severe foreign body reaction to the muslin.[99] Symptoms typical of the condition include headache, reduced visual acuity and afferent pupil defects. An abscess may develop and if the remaining muslin is removed and the abscess drained, vision improves.[100] Progressive cases with optic atrophy and severe visual field loss have also occurred following wrapping of aneurysms on the ophthalmic artery.[99] The vision loss is due to optic neuropathy secondary to muslin-induced arachnoiditis. Muslin causes thickening of the blood vessel wall and scarring of tissue. Histology

shows foreign body giant cells and inflammatory cells. Treatment is difficult as decompression can cause further visual loss[99] but steroid therapy has benefited some patients.[98]

Standard primary treatment for optochiasmatic arachnoiditis includes dexamethasone, warfarin and dipyridamole.[101] Surgical lysis of the adhesions has provided improvement of visual function in most patients at least in the short term[101-103] and use of cyclophosphamide has also been successful.[101]

In patients with optochiasmatic arachnoiditis, visual evoked cortical potentials (VECP), which depend on the functional integrity of the entire visual pathway from the eye to the primary visual cortex, are usually abnormal with increased latencies and reduced amplitudes.[95,104] VECP recordings can provide useful information on the prognosis of recovery during the postoperative period[104-106] as changes to VECP amplitude correlate to changes in visual acuity.[95]

1.3.2 Arachnoiditis Generalised to the Brain

There has been a recent resurgence of diffuse arachnoiditis caused by tuberculosis and cryptococcal central nervous system (CNS) infections which is in part attributable to the acquired immune deficiency syndrome (AIDS) epidemic.[107]

Findings of tuberculous arachnoiditis include photophobia, papilloedema, transient third and sixth nerve palsies, pupillary abnormalities, optic atrophy, reduced visual acuity and visual field defects. Vision is usually affected at the height of the disease and if optic atrophy ensues then prognosis for vision is not good.[108] MRI shows perichiasmal enhancement consistent with

a persistent inflammatory process in the chiasmatic cistern. Visual loss may be the result of this perichiasmal inflammatory process with a superimposed vascular insult to optic nerves, chiasm and tracts.[16]

Fungal infection by cryptococcus neoformans has also been reported with similar visual effects. Up to 40% of patients will have abnormal ocular findings including photophobia, diplopia, blepharoptosis, amblyopia, nystagmus, ophthalmoplegia, anisocoria, papilloedema, neuroretinitis and optic atrophy (Table 1.5).[109] Autopsy suggests that the atrophy may be the result of direct invasion and destruction of the optic nerve by the organism[109-111] however CT scans show adhesive arachnoiditis within the chiasmatic cistern. The operative view shows adhesive tissue strangling the optic nerve which, upon removal, improves vision.[112] Other cases have mild diffuse cerebral atrophy and normal optic nerves[113] again highlighting the individual variation of this inflammatory disease. In cases with sudden onset of visual loss a vascular compression of the nerve has been suggested as relief is gained by decompression.[113]

TABLE 1.5 ***Incidence of ocular findings in cryptococcal infection***[109]

Papilloedema	33%	Ocular palsies	14%
Blurred vision	27%	Optic atrophy	8%
Enlarged blind spot	25%	Diplopia	5%
Severe visual damage	16%	Photophobia	5%
Retrobulbar pain	14%		

There has also been speculation for some time that HIV+ patients have CNS involvement despite a lack of clinical symptoms.[114,115] Pattern visual evoked cortical potentials (PVECP) are usually normal in the early stages of HIV infection, but up to 4% of neurologically and ophthalmologically asymptomatic AIDS patients will have abnormal PVECP delays. HIV

entering the CNS soon after infection has been confirmed by observation of CSF anomalies in HIV positive patients. It is hypothesized that the visual involvement is related to the myelin pallor sometimes seen in AIDS patients.[114] Morphometric examination of optic nerves has shown axonal degeneration and a 40% reduction in total axonal population. The extent and pattern of loss suggests damage associated with a primary optic neuropathy.[116]

The amplitude of the pattern VECP diminishes with lowered cell counts (CD4) and improves with treatment. Thus the VECP not only monitors visual pathway dysfunction but also progression of the general disease.[117] Flash visual evoked potentials are highly variable and may show normal latency with significant amplitude reduction but later show increased latency with the amplitude restored.[17]

1.3.3 Adverse Visual Effects of Myelography

In regard to the known visual effects following myelography, there are three distinct periods in which they occur. Acute effects accompany the acute meningeal reaction within hours of the procedure, cranial nerve palsies can occur within the first week following the myelography and late visual effects associated with the chronic inflammatory reaction can develop weeks to months later. Cranial palsies and late visual effects may arise independently or follow the acute reaction.[118]

1.3.3.1 Cranial Nerve Palsies

It is clear that a contrast agent injected into the lower spine can reach the cranium as Myodil® has been noted on the dental x-rays of patient with

chronic headaches and jaw pain. Even after removal of the dye there is always a small amount of residual dye that can enter the brain.[48] As discussed earlier, this penetration of contrast agent into the brain has been explained by the finding that the CSF and the extracellular fluid spaces of the brain are continuous.[119] Arachnoidal reaction in the brain is most prominent around the brain stem which is significant due to the close proximity to the lower cranial nerves.[120]

One of the more common visual side effects of myelography is the development of ocular palsies, usually within the first few weeks following the myelogram.[121-123] It appears the palsy is attributable to both the contrast agent and the actual lumbar puncture procedure. Studies have shown that following lumbar puncture without myelography the incidence of sixth nerve palsy is approximately one in 400 procedures.[124] Third and fourth nerve palsies also occur and all recover by about four months.[125] For young adults the incidence of third, fourth and sixth nerve palsy has been reported as high as 4%.[126] The majority of patients with palsies experience diplopia[122,127-129] and temporary nystagmus has also been reported.[61,118]

Palsies following lumbar puncture are thought to be due to the leakage of CSF from the subarachnoid space which results in a caudal shift of the brain inducing traction on the cranial nerves.[124,125,130] Most of the cranial nerves can be affected but sixth nerve damage is by far the most common due to its vulnerable pathway within the brain.[124] The reduction in side effects with smaller diameter needles has in part proven this theory.[130]

But following myelography the incidence of palsy is higher still suggesting an additional toxic effect of the contrast agent.[123] The sixth nerves are in direct contact with CSF and any sixth nerve irritation can affect function of the lateral rectus muscle.[131] A neurotoxic spinal arachnoiditis has been implicated but such a diffuse inflammatory response can not alone explain

selective damage to one or more nerves.[122,129] The onset of the palsy should coincide with the contrast agent reaching the brain rather than a week or so later as commonly seen. If there was a direct toxic effect on the nerve or nucleus, a higher incidence of bilateral cases should be found, and in fact 75% are unilateral.[124] Possibly there is a partial physiological compromise of the nerve due to the contrast agent and this in combination with the CSF leakage syndrome may be sufficient to cause the palsy.[121,122]

1.3.3.2 Optic Nerve Involvement

Accidental demonstration of contrast agent in the optic nerve sheath has proven that contrast agent can move into the subarachnoid space of the optic nerves from the basal cisterns.[132] The contrast agent can fill the subarachnoid space to the scleral attachment of the dura mater at the posterior pole of the eye. In this particular case report there was no effect on vision and the contrast agent disappeared within 24 hours.

In contrast, studies in beagles following Pantopaque® myelography have showed a small focus of inflammatory cells in and around the dural sheath of the optic nerve accompanied by chronic inflammation of the conjunctiva.[59] Likewise, studies in cats have proven that there is risk of neuropathy following the use of lipid and water based dyes. The risk increases with high doses, multiple doses and lipid solubility of the dye. Histology showed arachnoiditis of the optic nerve sheath characterized by fibrosis and some infiltration of inflammatory cells. The subsequent optic nerve compression caused axonal swelling and demyelination consistent with early optic atrophy.[133]

There have also been reports of immediate and late visual effects following myelography in humans. Immediate reactions, which are either allergic or vascular, include allergic reactions of the conjunctiva and lids, flickering

lights and photophobia.[134] Late effects that involve the posterior visual pathways include reduced vision, red-green colour vision defects, scotomas and cortical blindness.[134] Optic nerve involvement is thought to be due to an inflammatory reaction to the contrast agent.[135] In support of this there has been a report of temporary unilateral visual loss related to droplets of iophendylate along the optic nerve[135,136] where CSF analysis ruled out existing demyelinating disease.[135] Residual Pantopaque® is often observed close to the optic chiasm in the basal cisterns and around the Circle of Willis.[137]

Water-based dyes at recommended doses also appear in the chiasmatic cistern and optic nerve sheath for about 30 minutes but usually without causing arachnoiditis.[138] Penetration there and into other parts of the brain may explain some of the visual complaints occasionally reported straight after water soluble myelography which include transient amaurosis,[139] nystagmus and visual hallucinations.[71,140] A report of ventriculitis with blurred vision lasting three months after a metrizamide myelogram[141] shows that there are still risks of chronic adverse effects with current dyes.

1.3.3.3 Visual Evoked Cortical Potentials

Optic involvement can be best evaluated by visual evoked cortical potentials which reflect the integrity of the entire sensory visual pathway.[142,143] Retinal involvement can then be excluded by establishing that electroretinograms are normal. Any motor involvement can be investigated by the recording of somatosensory potentials.

There is substantial electrophysiological evidence that contrast agents do affect nerve conduction in the immediate recovery period. Somatosensory potentials of cats show increased latencies and reduced amplitudes proportional to the toxicity of the contrast agent that has been injected.[144]

Other electrophysiological evidence of CNS irritation includes electroencephalograph (EEG) abnormalities recorded in humans after metrizamide myelography.[145]

Visual evoked potentials recorded at one and 20 hours after water soluble myleography showed changes correlated to symptoms of headache.[146] An increased latency was found at 20 hours which correlated to the presence of residual contrast agent in the CSF and to the extent of headache (Table 1.6). Sixty eight percent of patients experienced headache following metrizamide and 50% following iopamidol myelography. Control VECP data was recorded in patients who had a lumbar puncture only, giving a normal latency range of 85-105 milliseconds.

TABLE 1.6 ***Acute VECP delay following contrast myelography***[146]

Contrast Agent	Latency change at 1 hour *msec*	Latency change at 20 hours *msec* (SD)
Metrizamide	+1.5	+3.90 (2.91)
Iopamidol	+2.6	+2.03 (2.98)
Controls	+0.7	- 0.20

The delay in the VECP is related to how much of the dye reaches the cranium which in turn is dependent on dose, injection site, and manipulation of the patient during the procedure.[146,147] (See Table 1.7) It seems that the greatest risk is in patients who receive a large lumbar dose that travels rostrally and enters the brain, either intentionally for examination, or through a poor recovery procedure of the patient.

TABLE 1.7 ***Dose and procedural related effects of metrizamide and iopamidol on VECP delay at 20 hours***[146]

Injection Site	Examination Site	Concentration *mg/mL*	Maximum Dose *mL*	Latency Increase *msec*
Metrizamide				
Lumbar	Lumbar	170	17.7	2.5
Lumbar	Cervical	170	17.7	5.7
Cervical	Cervical	300	5-7	3.5
Iopamidol				
Lumbar	Lumbar	300	13.0	1.2
Lumbar	Cervical	300	13.0	2.4
Cervical	Cervical	300	8.0	2.5

Similar findings for iopamidol and iohexol have also been found when VECPs were measured at six and 24 hours. Abnormal delays were recorded in 70% of patients following iopamidol and 40% of patients following iohexol myelography.[148]

Although these acute VECP effects are fairly well accepted there has been little investigation of the VECP in chronic arachnoiditis. An isolated case report describes a patient who developed adhesive basal arachnoiditis with nystagmus and a number of other neurological signs.[61] Iophendylate droplets were found in the subarachnoid space of the supratentorial and infratentorial compartments, the Sylvian fissures, the optochiasmatic, quadtrigeminal and cerebello-medullary cisterns. There was mild distortion of the posterior fossa structures especially over the right cerebellomedullary cistern. VECPs were bilaterally prolonged to 118 milliseconds and 111 milliseconds with an upper limit normal value of 108 milliseconds for that laboratory. A normal CSF ruled out chronic meningitis. Delayed VECPs in the presence of normal visual acuity suggested subclinical optic nerve lesions due to basal cisternal arachnoiditis.[61]

1.4 COMPARISON OF ARACHNOIDITIS TO MULTIPLE SCLEROSIS

1.4.1 Multiple Sclerosis

Although little is known about the visual system in chronic arachnoiditis, some insight may be gained by reviewing other demyelinating diseases that are known to affect vision, such as multiple sclerosis.

Multiple sclerosis (MS) is a slowly progressive disease of the central nervous system characterized by disseminated patches of demyelination in the brain and spinal cord. These lesions result in multiple and varied neurological symptoms and signs usually with remissions and exacerbations.[149,150] There are sudden and sporadic appearances of minute areas of inflammation within the CNS which cause symptoms associated with that area of control. Episodes are temporary but function does not always return to the original level. A diagnosis is made by the existence of a number of neurological signs disseminated over the body at different times.[151] Diagnosis may be aided by MRI, abnormal VECPs or CSF findings.[152] Many signs are so transient and benign that the patient may not even recall them. Symptoms can include diplopia, ataxia, vertigo, paresthesis, bladder dysfunction, bowel dysfunction and extremity weakness. Because symptoms are not always accompanied by objective signs, the patient may be labeled hysterical. Unlike arachnoiditis however, pain is infrequently seen.[153]

The cause of multiple sclerosis is not known, but an immunological abnormality is suspected. Women are affected twice as often as men, there is a increased family incidence, and it is more common in temperate climates than in the tropics.[149,154] Migration studies show that it is the native location during childhood that carries the risk, suggesting both a genetic and environmental factor. Maybe an acquired agent such as a virus precipitates an autoimmune process that attacks myelin. The prevalence in the US

varies from 6-80 per 100000, being uncommon under the age of ten years and mainly in the 25 to 40 year age group.[155]
Perivascular inflammation and plaques of demyelination are primarily in the white matter of the CNS and show a predilection for the lateral and posterior columns of the cervical and dorsal regions, the optic nerves and the periventricular areas. Tracts in the midbrain and pons can also be affected. There are chemical changes in the lipid and protein of the myelin, however initially cell bodies and axons are preserved.[149,153]

There is no successful treatment for reversing or even arresting multiple sclerosis.[150] Steroids are often used in the acute phase of an attack and interferon beta reduces attacks in remitting cases.[149,154]

1.4.2 Similarities of Multiple Sclerosis and Arachnoiditis

The overlap of arachnoiditis and multiple sclerosis is apparent in the current study as many of the arachnoiditis subjects have at one point been erroneously diagnosed with multiple sclerosis. The corollary is true that many idiopathic optochiasmatic arachnoiditis cases are later found to be caused by multiple sclerosis.[156] Both arachnoiditis and multiple sclerosis patients share the commonality of an inflammatory focus, nerve demyelination and a suspected foreign body and immune reaction.

It is interesting that patients with multiple sclerosis frequently develop acute aseptic meningitis and arachnoiditis following myelography. Up to 12% of patients with multiple sclerosis have arachnoiditis type symptoms. MS patients also suffer more severe headaches following lumbar punctures and they have increased sensitivity to all intrathecally injected substances including corticosteroids.[33,50]

Multiple sclerosis patients also experience diplopia. However because MS is a disease of the CNS, motility abnormalities are typically localized to the supranuclear, nuclear and fascicular portions of the ocular motor system, rarely affecting peripheral nerves. If ocular motor palsies occur they are accompanied by brain stem findings. Most common is a sixth nerve palsy and sometimes a third nerve palsy.[128]

1.4.3 Visual Loss in Multiple Sclerosis

As multiple sclerosis has a predilection for the optic nerves, optic neuritis is common. The resolved inflammation leaves scarring which can usually be sighted on MRI. A quarter of cases present with optic neuritis and eventually 70% of patients will experience optic neuritis. Between 50 and 70% of patients with optic neuritis are diagnosed with multiple sclerosis within five years. About 20% of patients have a benign course with little or no disability while ten percent have a progressive course ending in severe disability. The remaining group have recurrent attacks with clear periods in between.[154]

Clinically the patient complains of a loss of vision in a quiet eye over a short period of time. There is variable visual acuity reduction, central scotoma, a loss of brightness and desaturation to red. An afferent pupil defect persists during the active phase with an increase in latency of the VECP. Retrobulbar neuritis causes pain on eye movement as the swollen nerve is rubbed against the surrounding muscles. If the optic nerve head is involved atrophy results. Usually visual acuity recovers in a few weeks, but contrast sensitivity, colour vision, visual fields and the VECP may remain abnormal.[154,157] Nystagmus is quite common but permanent pupillary abnormalities and blindness are rare.[149]

A study that investigated the appearance of MRI and CT scans where visual field loss existed found a lesion in 17/18 cases. The lesion is generally large enough to be detectable on CT scan alone. Lesions can involve the optic nerve, the tract, the lateral geniculate nucleus, the optic radiations or cortex. Complete recovery of the visual field occurs in most cases.[158]
Treatment of optic neuritis with oral prednisolone does not improve visual outcome and in fact is associated with recurrent attacks of optic neuritis.[157] Treatment with high dose intravenous methylprednisone followed by oral prednisolone accelerates visual recovery but likewise is unable to provide any long term benefit to vision.[157,159]

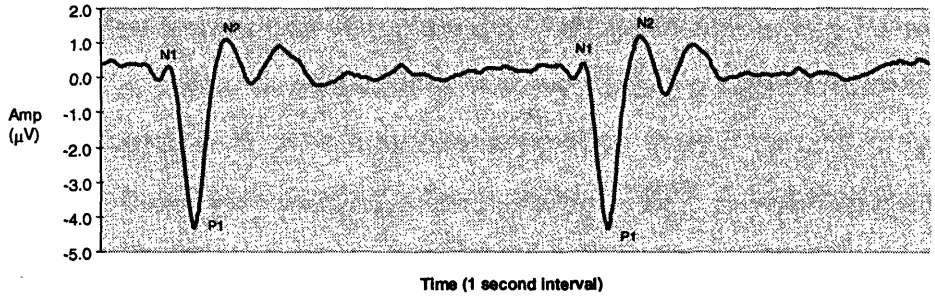
1.4.4 Visual Evoked Potentials in Multiple Sclerosis

Patients with multiple sclerosis can have visual involvement that is not clinically apparent. The detection of this hidden visual loss can be important in establishing the diagnosis of multiple sclerosis in patients who have other neurological symptoms suggestive of the disease.[160,161] Visual evoked potentials, contrast sensitivity, colour vision and visual field testing have been used for this purpose, with VECPs being the most sensitive test.[162] VECP abnormalities, which include increased latency of the major peaks (N1 and P1) and reduced amplitude of the major positive peak (P1) occur in 94% of unaffected eyes, while contrast sensitivity (Vistech VCTS) is abnormal in only 50% of patients. See Figure 1.3 for identification of the VECP major peaks.

A 48' size stimulus is considered optimal for detecting abnormalities, however using a number of different stimuli will increase the rate of diagnosis.[160] The VECP is useful in showing the disseminated nature of the disease, particularly when symptoms suggest only an isolated lesion away from the visual pathway.[163]

FIGURE 1.3 Typical VECP Waveform Showing Major Peaks

2 waveforms are displayed, inverted by convention.



1.4.4.1 VECP Latency

The single most common deviation of the VECP to patterned stimuli is prolongation of the latency of P1. Ruessmann reports that 77% of MS patients will have a delayed P1 and 32% will have a significant inter-ocular difference giving a combined abnormality rate of 83%.[164] When judging the abnormality of the VECP by P1 latency only, about five percent of patients with optic neuritis or past episodes of optic neuritis will appear normal.[163,165]

By including analysis of the first negative peak (N1) the VECP gives a higher diagnostic yield, as N1 is derived from different visual processes to P1. Patients with optic neuritis usually have a delayed P1 and a delayed or absent N1. These delays are noted even in eyes without clinical evidence of optic neuritis but with greater discrepancies between the two peaks. The P1 will be closer to the upper limit of normal while the N1 will still be significantly delayed or absent.[166] Halliday reports a mean increase in P1 latency of 35 milliseconds[167] but it can be delayed up to 150 milliseconds.[168]

1.4.4.2 VECP Amplitude

Amplitude of either peak may also be reduced regardless of stimulus and is correlated to reduced visual acuity. Amplitude alone may be reduced in the case of a partial demyelinating lesion where a group of normally conducting fibres remain. N1 has a smaller amplitude than P1 which may explain why N1 can be absent despite a fairly normal P1.[169] A reduced amplitude of the P1 can be misleading as the P2 may erroneously be labeled as a delayed P1. Measurement of latency is also complicated by an abnormal shape of the waveform.[150]

1.4.4.3 VECP Recovery

When latency is prolonged it only improves to normal in about ten percent of cases and may take many years. Latency increase is more likely related to demyelination and this longer period of recovery may represent repair of myelin or axon damage. When the disease is disseminated there is an increased delay compared to straight isolated optic neuritis but the recovery is faster.[163,170] If amplitude is reduced it recovers over weeks in parallel to the recovery of visual acuity.[170] As acuity and latency appear unrelated, acuity can improve while latency remains delayed and vice versa. [150] Acuity does improve in 50 to 80% of patients within six months of the attack.[171]

The temporary reduction in amplitude is most likely caused by conduction block secondary to swelling and oedema of the nerve, whereas the ongoing increase in latency is probably related to the length of the demyelinated plaque which does not recover, at least in the short term.[172]

1.4.4.4 Flash VECP

There are conflicting reports of the value of flash VECPs. Some laboratories claim the high variation amongst normal subjects makes flash VECPs unreliable. To overcome this, Wilson and Keyser used a very stringent definition of abnormal and found a delayed P1 in 80% of MS patients.[150] Latency of the flash response shows an increase between ten and 18 milliseconds which is not as delayed as the pattern response. The flash response amplitude is dramatically affected in the acute phase but recovers more rapidly than the pattern response. Amplitude of the flash response is also reduced in the unaffected eye.[167]

The differences between the pattern and flash delays may be explained by the fact that the pattern response originates mainly from the central retina and the flash response is more peripheral. The larger fibres of the peripheral retina have a greater conduction velocity and will have fewer nodes involved in the demyelinated zone, hence a smaller delay.[163]

1.4.4.5 Interpretation of VECP Findings

Although VECPs are a reliable determinant of CNS disturbance they do not discriminate between multiple sclerosis and other non MS disease. To make this differentiation the CSF must be analysed to find a characteristic immunoglobulin production that occurs in MS. The VECP however is abnormal in 64-94% of patients with MS but only 15% of suspected MS patients have abnormal VECPs.[152,160,167,173] The wide range of abnormalities reported probably relates to patients in different phases of the disease[170] and the use of different stimuli and methods of analysis. Transient pattern VECPs are considered most effective[174] although flicker evoked potentials may be more sensitive in the early phases of MS.[161]

1.4.4.6 VECP and Visual Field Loss

How lesions in the visual pathway translate to visual field defects is unpredictable. Plaques are found throughout the visual pathway but homonymous visual field loss due to posterior pathway defects are rare. Investigation of the posterior pathways using VECPs is also difficult due to the poor sensitivity of hemifield VECPs in detecting postchiasmal lesions. The increased diagnosis of anterior damage may be because the nerve fibres are more compact in this part of the pathway making them more susceptible to oedema.[158]

1.4.5 Visual Reaction Time in Multiple Sclerosis

Unprepared simple visual reaction time (VRT) is the time required for a subject to respond to a visual stimulus, by depressing a button, following a variable waiting period.[175] Since multiple sclerosis affects sensory and motor nerve conduction, visual reaction time can therefore be affected.

For normal subjects, fastest reaction times are generally recorded during the twenties and increase over life by an average of 35 milliseconds. A statistically significant difference only occurs between the twenties and the over fifties. Variability also increases with age but again this is not significant until over age seventy.[175]

When VRT is measured in MS patients there is an increase in delay compared to controls which is related to disease duration and the simultaneous presence of brain stem, cerebellar and/or pyramidal signs. For each year of disease duration there is a five millisecond increase in delay. Since delayed VRT is not found to be correlated to visual impairment and complex VRT is no more delayed than simple VRT, the delay is more likely

due to motor input rather than cognitive. It follows that the VRT measured after prolonged mental effort to induce fatigue produces no more additional delay than in controls.[176,177] At least this is true in the early stages of the disease.

Eventually up to 50% of patients exhibit some degree of cognitive deficit which is usually related to disease advancement. In these patients, when scanning rate is measured in addition to VRT, a measure of pure cognitive speed is being made, which is significantly slower than controls. If more memory is required to do the VRT task then a longer VRT results. This is probably related to the "subcortical dementia" that is suspected with widespread involvement of the white matter.[178] When patients have to make a choice before reacting delays can exceed 420 milliseconds.[179]

1.5 SUMMARY

From the known visual symptoms of acute arachnoiditis and the understanding of the inflammatory nature of chronic arachnoiditis, it is hypothesised that patients with chronic arachnoiditis could have chronic visual involvement manifesting as a low grade optic neuritis.

This involvement is likely in Myodil® arachnoiditis as the continuous nature of the subarachnoid spaces would allow a contrast agent to remain in close proximity to the visual pathway for many years after the myelogram procedure. The extent of visual pathway involvement should be related to the level of arachnoiditis in the brain and it is unlikely that patients with arachnoiditis limited to the lumbo-sacral area would show any visual defects. Since the underlying process in arachnoiditis is demyelination, this study was designed to evaluate the visual functions that are commonly abnormal in multiple sclerosis. It is expected that the visual evoked potentials will

have increased latencies and reduced amplitudes for both the first negative and positive peaks and visual reaction time should also be delayed.

Electrophysiological changes may be present even in the absence of clear clinical signs but for subjects with monocular symptoms it is anticipated that the symptomatic eye will have the more significant changes.

CHAPTER 2: MATERIALS & METHODS

2.1 SUBJECTS

As the normal VECP is influenced by subject age and test conditions, a test and a control group were used. Test group subjects were 3 males and 8 females aged between 42 and 72 years recruited through referrals and newspaper advertising. Eligible subjects had a positive diagnosis of arachnoiditis either focal to the lumbar spine or diffuse to the CNS. All subjects had a history of Myodil® myelography for examination of the lumbar spine. Diagnosis had been confirmed by myelogram, contrast enhanced CT scan or MRI. The subjects had a history of arachnoiditis ranging between six and 24 years. All patients were ambulatory but many relied on a walking stick. Subjects were assigned to a subgroup of either focal or diffuse arachnoiditis according to the established diagnosis.

Control group consisted of 15 healthy individuals ranging in age from 27 to 73 years. Apart from slight refractive errors, which were corrected, all controls were free of visual impairment. Controls were matched for age and sex where possible.

TABLE 2.1 ***Sex and age of subjects by group***

	Control		Focal		Diffuse		Sig. Level*
	n	%	n	%	n	%	Fisher's Exact
Male	9	60	2	66.6	2	25	p=0.371
Female	6	40	1	33.3	6	75	
	Mean	SD	Mean	SD	Mean	SD	Kruskal Wallis
Age (years)	52.8	12.8	50.7	9.6	57.9	7.0	p=0.674
	Mean	SD	Mean	SD	Mean	SD	Mann-Whitney U
Disease Duration (yrs)	-	-	18.7	6.1	16.8	6.4	p=0.630

*comparisons are between all groups except for disease duration which compares focal and diffuse groups only; significance level was $p<0.05$, therefore all results are not significant

2.2 DATA COLLECTION

The methods used in this study are well established clinical techniques used in a standard optometric examination of humans. All techniques were carried out in identical conditions for both the test and control groups. The complete testing of each subject was conducted on the same day. All subjects were examined within a three month period.

Due to the disability associated with arachnoiditis and the number and length of procedures carried out, precautions were taken to avoid subject discomfort and fatigue. The protocol was designed so that the longest period a subject had to sit for uninterrupted was 2 minutes. All subjects were permitted to stand up and stretch between procedures as well as between each VECP recording. No patient actually required a pause during testing, however the arachnoiditis patients did require longer periods of rest between procedures.

2.3 STANDARD CLINICAL ASSESSMENT

The following data were collected:

a) basic ocular history and symptoms (without prompting)
b) corrected visual acuity (Reichert Selectra POS projector, 22.5 cd/m^2)
c) corrected visual acuity on a low contrast Bailey-Lovie Chart (19.0 cd/m^2)
d) contrast sensitivity at 1 metre, measured in log contrast sensitivity, using the Pelli-Robson Chart (37.8 cd/m^2)
e) pupil reactions to detect afferent pupil defects
f) ocular motilities and red lens test to detect palsy
g) biomicroscopy assessment of the cornea and crystalline lens to establish that media were clear prior to VECP recordings

h) direct ophthalmoscopy to evaluate the optic disc

i) monocular colour vision using the L'Anthony Desaturated D-15 (32 cd/ m^2).

Colour vision results were recorded using the Vingrys & King-Smith method. This method yields a C-index, representing a measure of total errors made and a S-index, indicating the polarity of those errors.[180]

Visual field testing was not included in the protocol as most arachnoiditis subjects were unable to sit for extended periods.

All luminance values were measured using a Tektronix J16 Photometer (J6523-2 10 degree Narrow Angle Luminance Probe) with a calibration error of 9%.

2.4 ELECTROPHYSIOLOGICAL ASSESSMENT

Transient visual evoked cortical potentials were recorded using stimuli presented on a high resolution monochrome display subtending 15 x 15 degrees at a one metre test distance. The spaced averaged background luminance of the monitor was 81 cd/m^2 and the ambient room illumination was 5.7 cd/m^2 (semi darkened room). Subjects were refracted to best acuity at the test distance and were instructed to fixate on a small target (4.0 mm diameter) at the center of the monitor. The experimenter visually monitored visual fixation throughout the test procedure and was able to temporarily stop recording if necessary.

VECPs were recorded from surface electrodes placed 2 centimetres above the inion (Oz) on the midline and referred to a similar electrode placed at the vertex (Cz). The skin was prepared by rubbing with isopropyl alcohol.

Electrodes were attached with a water based conducting paste (Meditrace). An ear electrode served as a ground. Impedance of each cup electrode was below 5 K ohms. The frequency response of the recording system (ENFANT™ 4010 Visual Stimulator / Electrophysiological Assessment System, Neuroscientific Corp.) was 3.2 to 80 Hz. Analysis time for each recording was one minute. A low pass cutoff filter of 49.5 Hz, provided by the software, was applied to all recordings. An optimize function temporarily removed each record one at a time and dropped the record permanently if the confidence level tightened. Three recordings of at least 100 averaged responses were made for each stimulus, for each eye. Table 2.2 lists the characteristics of each stimulus used. The recordings were stored on floppy disk

TABLE 2.2 ***Stimuli characteristics used for the transient visual evoked cortical potentials***

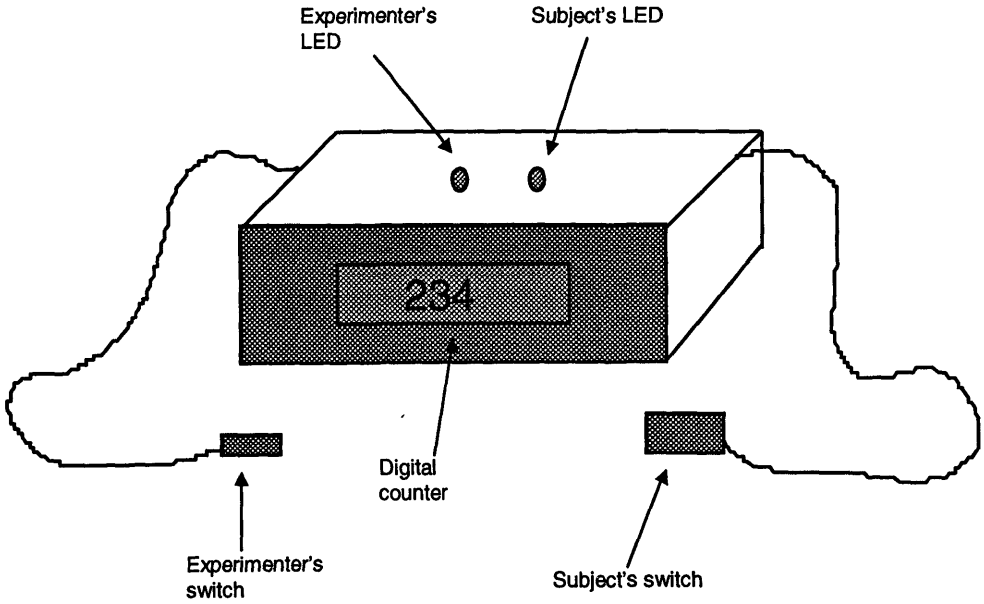
Stimulus Type	Check Size (min arc)	Temporal Frequency (Hz)	Luminance (cd/m^2)	Modulation Contrast (%)
Large Check	55	2	55 (white) 6 (black)	80
Small Check	27.5	2	55 (white) 6 (black)	80
Flash	-	1	68	-

2.5 VISUAL REACTION TIME

Monocular visual reaction times (VRT) were recorded using a commercially available light emitting diode (LED) counter kit with the provision of gating the clock counter. All subjects were read a standard set of instructions prior to recording. The experimenter pressed a switch which turned off a red LED

and started the count in millisecond increments. The subject responded to this by pressing a switch "as soon as they noticed the test LED had been extinguished" which stopped the counter and held the display visible (Figure 2.1). Testing was at one metre using the same lighting conditions and subject correction as for the VECP recordings. The inter-trial interval varied randomly between two and ten seconds. Ten responses were recorded for each eye following two practice runs for each eye. The subject viewed the readings for each practice trial but could not see the counter during the test trials. Trials where the subject obviously "was not ready" were discarded as were "false start" trials where corrected recordings were shorter than 120 milliseconds. The switch was designed so that muscular effort and time to move the switch would have contributed relatively little to the result.

FIGURE 2.1 ***Visual reaction time apparatus***



2.6 DATA ANALYSIS

Data analysis was performed using SPSS® for Windows™ Release 6.0 using an IBM Thinkpad personal computer. Eyes were analysed separately to avoid correlation that generally exists between two eyes of a single

subject. As eyes were analysed separately, number of subjects rather than number of eyes were used in the data analysis.

Since effects can be unilateral, results are reported as "best eye" and "worst eye" as there was no reason to assume that either eye was more at risk. The best eye was defined as the eye with the shortest mean VRT result.

2.6.1 Standard Clinical Assessments

Non-parametric tests were used for analysis as the data was not normally distributed. Chi squared (cross tabulation form) was used for all nominal measures. Kruskal-Wallis test was used for all other data followed by the Mann-Whitney U test (with Bonferroni correction) for post-hoc comparisons.

2.6.2 Electrophysiological Recordings

For the pattern VECPs, the three most prominent peaks, N1, P1 and N2 were identified from each recording. Latencies for N1, P1 and N2 were measured and inter-peak latencies were then calculated. For the flash VECP, the same labeling system was used so that the main positive peak that occurs at approximately 100 milliseconds was also labeled as P1.

Amplitudes were measured for the N1 and P1 peaks for all stimuli. Amplitudes were measured as peak to peak values as some records showed significant drift from baseline.

The Friedman test was used to establish any difference within repeat measurements. No significant difference between repeated measurements provided justification to use the mean of the repeat measurements to carry

out comparisons between groups. When within-subject differences existed, comparisons were made using analysis of variance (ANOVA) with repeated measures as there is no simple non-parametric test available for repeated measures.

Individual results were considered as abnormal if the P1 latency was greater than two standard deviations above the control mean. Only the P1 peak was considered as inclusion of all three peaks would have increased the false positive rate, particularly if there is a high correlation between the peaks.[181]

To identify potential changes to other parts of the waveforms, such as changes to the early wavelets that precede N1, a grand average waveform of each subject group was produced for each stimulus.

2.6.3 Visual Reaction Times

The Friedman test showed that there was no difference in repeat measurements. This justified the use of the visual reaction time mean, which was analysed using the Kruskal Wallis test and the Mann-Whitney U test for post-hoc comparisons.

Single fastest VRT was assessed in an attempt to identify a measure of reaction time that was least affected by the subject's ability to attend. Fastest reaction time data was also compared using the Kruskal-Wallis test and the Mann-Whitney U test.

Correlation analysis for all data was performed by the Spearman correlation method and the significance level for all tests was $p<0.05$. Exact p values (true distribution) were used when samples were unbalanced or small.

CHAPTER 3: RESULTS

3.1 Standard Clinical Assessments

3.1.1 History

Seven subjects reported non specific ocular symptoms that included pain in or around eye, dimming of vision or intermittent blurring of vision (Table 3.1). From this group, one focal subject and five diffuse subjects reported unilateral symptoms. One such diffuse subject (female) had a seven year history of optic neuritis of unknown aetiology. Another female reported a five year history of monocular "blacking out of vision". Both these females were shown to have abnormally delayed VECP latencies in the ipsilateral eye.

TABLE 3.1 ***Incidence of ocular symptoms reported by arachnoiditis subjects***

Symptoms Reported	Focal Arachnoiditis n=3		Diffuse Arachnoiditis n=8	
No ocular symptoms	2 subjects		1 subject	
	Unilateral	Bilateral	Unilateral	Bilateral
"Pain/burning in or behind eyes"	1		3	2*
"Vision dimming/blacking out"			2	
"Intermittent blurring"				1*

*one subject reported both symptoms

All arachnoiditis subjects reported long histories of pain management which included the use of oral analgesics, morphine pumps and in one case, the use of a dorsal column stimulator. In addition, patients with diffuse arachnoiditis, reported the use of medications for conditions believed to be secondary to the arachnoiditis, such as depression, anxiety, epilepsy and vertigo (Table 3.2). Apart from accommodation, ocular side effects of these drugs are unusual except that diazepam and sodium valproate can reduce or "normalise" the flash VECP which is often abnormally large in these

patients.[182] In this study, only 2 patients were taking diazepam and only one was taking sodium valproate.

TABLE 3.2 ***Medications used by the arachnoiditis subjects***

Condition	Generic (brand)
Pain (analgesics)	dextropropoxyphene /paracetamol (Di-gesic) paracetamol (Panadeine) methadone hydrochloride 10mg (Physceptone) codeine phosphate /paracetamol (Panadeine Forte) morphine sulfate (MS Contin) morphine pump (1mg/day) ibuprofen (Brufen)
Epilepsy	sodium valproate (Epilim) clonazepam (Rivotril)
Depression/Anxiety	amitripyline (Tryptanol) dothiepin (Prothiaden) diazepam (Valium)
Multiple sclerosis (voluntary muscle relaxant)	baclofen (Lioresal)
Vertigo	betahistine dihydrochloride (Serc)

Two subjects from the diffuse group reported balance difficulties that were apparent when walking. One of these subjects felt the difficulties with balance were associated with "an imbalance of vision".

Most patients described in one form or another the classic arachnoiditis symptom of "a burning feeling in the ankles and feet as if walking on rocks or glass".

3.1.2 Acuities and Contrast Sensitivity

There was no significant difference in high and low contrast visual acuity between groups (Table 3.3). There was also no difference in high and low contrast acuity between best and worst eye for all groups. There was however a significant reduction in high contrast acuity of symptomatic eyes compared to non symptomatic eyes within the arachnoiditis groups (p=0.025). See Table 3.4.

TABLE 3.3 ***High contrast acuity (VA), low contrast acuity (LCVA) and contrast sensitivity (CS) by groups***

	Control n=15		Focal n=3			Diffuse n=8		
BEST EYE	Mean	SD	Mean	SD	pvalue	Mean	SD	pvalue
VA *(logMAR)*	0.01	0.07	0.04	0.05	NS	0.03	0.03	NS
LCVA *(logMAR)*	0.29	0.13	0.24	0.11	NS	0.32	0.11	NS
CS *(log contrast)*	1.58	0.14	1.60	0.09	NS	1.48	0.10	NS
WORST EYE	Mean	SD	Mean	SD	pvalue	Mean	SD	pvalue
VA *(logMAR)*	0.02	0.07	-0.01	0.01	NS	0.05	0.03	NS
LCVA *(logMAR)*	0.30	0.12	0.22	0.11	NS	0.34	0.06	NS
CS *(log contrast)*	1.60	0.14	1.55	0.17	NS	1.46	0.07	0.016*

*significantly different from control value, p<0.05, NS = not significant (Kruskal Wallis test and Mann-Whitney U post-hoc comparisons)

Contrast sensitivity was significantly reduced for the worst eye of the diffuse arachnoiditis group compared to all other groups (p=0.016), however, unlike acuity, this reduction was not necessarily related to the symptomatic eye (Table 3.4). Again, there was no difference in the contrast sensitivity between the best and worst eye for all groups.

There was no significant correlation between visual acuity, low contrast acuity or contrast sensitivity with the duration of disease.

TABLE 3.4 ***High contrast acuity (VA), low contrast acuity (LCVA) and contrast sensitivity (CS) of symptomatic eyes versus non-symptomatic eyes in arachnoiditis subjects***

	Non-symptomatic Eye n=12 eyes		Symptomatic Eye n=10 eyes		
	Mean	SD	Mean	SD	pvalue
VA *(logMAR)*	0.02	0.03	0.05	0.04	0.025*
LCVA *(logMAR)*	0.29	0.09	0.31	0.11	NS
CS *(log contrast)*	1.52	0.09	1.47	0.12	NS

*significantly different from control value, $p<0.05$, NS = not significant (Mann-Whitney U test)

3.1.3 Pupils, Palsies and Optic Discs

Only subjects from the diffuse group showed any pupil, motility or optic disc abnormalities. The patient with the diagnosed optic neuritis showed an afferent pupil defect, pallor of the optic disc and abnormally increased VECP latencies of the same eye.

Another female subject showed bilateral optic pallor, bilaterally delayed VECPs and a third nerve palsy (without apparent pupil involvement) of the eye with the longer visual reaction time. Ptosis of the right eye increased on abduction.

A third female subject, with bilaterally delayed VECP latencies, showed unilateral optic disc pallor in the eye which had the longer latencies.

3.1.4 Colour Vision

There was no statistical difference of the C and S indices between groups. There was also no difference between best and worst eye for all groups. (See Table 3.5)

TABLE 3.5 ***L'Anthony desaturated D-15 colour vision of groups expressed as C (confusion) and S (specificity) indexes***

	Control (n=15)		Focal (n=3)			Diffuse (n=8)		
BEST EYE	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
C index	1.23	0.39	1.13	0.15	NS	1.28	0.40	NS
S index	2.28	0.36	2.43	0.35	NS	2.19	0.35	NS

WORST EYE	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
C index	1.24	0.38	1.23	0.15	NS	1.23	0.12	NS
S index	2.35	0.37	2.20	0.20	NS	2.33	0.10	NS

p values show significant difference from control, $p<0.05$, NS = not significant

(Kruskal Wallis test and Mann-Whitney U post-hoc comparisons)

3.2 Electrophysiological results

3.2.1 Controls

N1 and P1 could be identified in all subjects for all stimuli. Repeated measurements showed within-subject consistency for the small checkerboard stimulus but differences for the large checkerboard N1 latency and flash P1 latency (Appendix 1.5). As there was some variability in repeated measurements for an individual subject, instead of comparing the average measure for each subject, comparisons were made using ANOVA with the repeated measures option.

There were no differences between best and worst eyes but differences between the sexes (Table 3.6). Mean latencies for N1 and P1 were shorter for males compared to females but the standard deviation was larger among males. This difference was only statistically true for the large check P1 latency (best eye, p=0.051, power=0.511; worst eye, p=0.017).

TABLE 3.6 ***Average VECP latencies and amplitudes of control group to the large (55 min arc) checkerboard stimulus***

BEST EYE	Males (n=9)		Females (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	80.2	9.6	83.7	8.6	NS
P1	107.5	4.0	110.7	3.4	0.051*
N2	144.3	10.4	149.6	6.9	NS
N1-P1	27.3	9.1	27.0	7.1	NS
P1-N2	36.7	12.2	38.9	8.1	NS
N1-N2	64.0	16.7	65.9	11.8	NS
Amplitude *(μV)*					
N1	-1.2	0.9	-2.5	1.7	NS
P1	4.6	2.3	7.5	3.4	NS

WORST EYE	Males (n=9)		Females (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	79.2	11.3	84.3	8.3	NS
P1	107.1	4.0	111.4	4.1	0.017
N2	142.7	10.8	149.1	6.9	NS
N1-P1	27.9	11.2	27.1	7.0	NS
P1-N2	35.6	10.8	37.7	7.0	NS
N1-N2	63.6	16.3	64.8	11.0	NS
Amplitude *(μV)*					
N1	-1.4	1.1	-3.0	2.0	0.035
P1	4.3	1.6	8.0	3.9	0.022

*May be significant as power low at 0.511 .Significance level p<0.05,

NS = not significant (ANOVA with repeated measures)

Female control subjects showed amplitudes up to double the size of male control results. This difference was statistically significant for the large check N1 and P1 peak (worst eye p=0.035 and 0.022 respectively) and for the small check N1 peak (worst eye p=0.048).

TABLE 3.7 ***Average VECP latencies and amplitudes of control group to the small (27.5 min arc) checkerboard stimulus***

BEST EYE	Males (n=9)		Females (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	82.8	6.8	85.2	7.8	NS
P1	107.7	4.7	111.6	5.6	NS
N2	144.6	6.9	147.2	8.5	NS
N1-P1	24.9	7.1	26.4	6.6	NS
P1-N2	36.9	7.8	35.6	9.2	NS
N1-N2	61.8	10.5	62.0	10.0	NS
Amplitude *(μV)*					
N1	-1.6	1.1	-3.00	2.1	NS
P1	5.1	2.0	7.6	3.5	NS

WORST EYE	Males (n=9)		Females (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	80.7	9.2	87.5	7.6	NS
P1	108.4	5.3	112.2	5.4	NS
N2	144.6	8.7	147.3	6.2	NS
N1-P1	27.7	10.2	24.7	6.2	NS
P1-N2	36.2	9.6	35.1	8.0	NS
N1-N2	64.0	13.9	59.7	9.6	NS
Amplitude *(μV)*					
N1	-1.5	1.0	-2.8	2.0	0.048
P1	5.1	2.4	7.3	4.1	NS

Significance level p<0.05, NS = not significant

(ANOVA with repeated measures)

The flash waveforms showed large individual variations and no statistical differences between the sexes (Table 3.8).

TABLE 3.8 ***Average VECP latencies and amplitudes of control group to the flash stimulus***

BEST EYE	Males (n=9)		Females (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	81.1	9.0	71.8	10.3	NS
P1	112.6	10.4	107.8	14.2	NS
N2	148.0	16.8	161.4	14.9	NS
N1-P1	27.4	19.4	33.2	29.7	NS
P1-N2	32.8	17.2	56.3	32.6	NS
N1-N2	60.2	26.5	89.5	21.2	NS
Amplitude *(μV)*					
N1	-2.4	1.3	-2.9	2.0	NS
P1	5.0	2.7	6.3	4.2	NS

WORST EYE	Males (n=9)		Females (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	82.7	9.7	72.4	10.5	NS
P1	113.7	11.1	108.0	15.6	NS
N2	149.8	19.0	160.4	14.6	NS
N1-P1	28.2	19.2	30.4	29.5	NS
P1-N2	31.3	16.3	57.6	32.1	NS
N1-N2	59.5	26.4	88.0	21.7	NS
Amplitude *(μV)*					
N1	-2.5	1.5	-2.6	1.9	NS
P1	5.1	2.6	5.4	3.2	NS

Significance level $p<0.05$, NS = not significant

(ANOVA with repeated measures)

3.2.2. Test Groups

There were no significant differences between the focal arachnoiditis and control groups. For the diffuse arachnoiditis group the males always had shorter latencies but greater standard deviations than females. These differences were not statistically different due to the low number of males.

In comparing the diffuse arachnoiditis group to controls, there was generally an increase in latency and reduction in amplitude of the diffuse arachnoiditis waveforms. The most common statistically significant difference was for P1 latency. N1 was present in all subjects but again typically smaller in diffuse arachnoiditis subjects. The most common abnormal constellation of P1 and N1 was a prolonged latency of P1 and a reduced amplitude of N1. Examples of recordings are shown in Figure 3.1, 3.2 and 3.3.

FIGURE 3.1 ***Example pattern VECP (27.5' check) of a control subject (VA 6/6)***

Result shows 2 traces, inverted by convention, and with the major positive peak (P1) marked. P1 is approximately 110 msec.

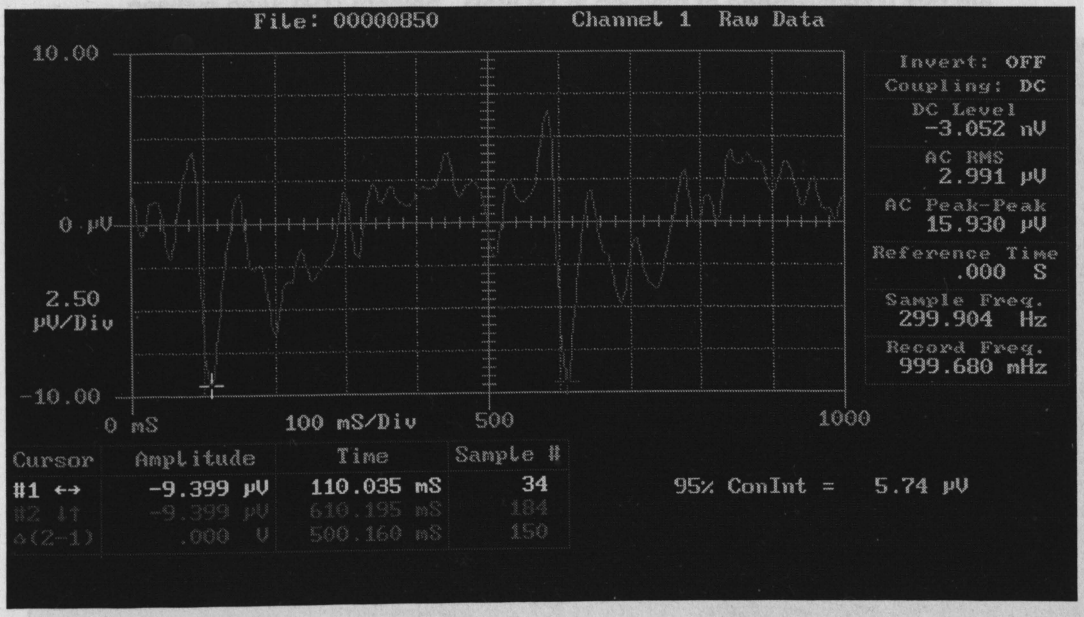


FIGURE 3.2 ***Example pattern VECP (27.5' check) of a sex and age matched diffuse arachnoiditis subject (VA 6/7.5)***

Result shows 2 traces, inverted by convention, and with the major positive peak (P1) marked. Note the reduction in amplitude of the positive and negative peaks compared to the control result shown in Figure 3.1.

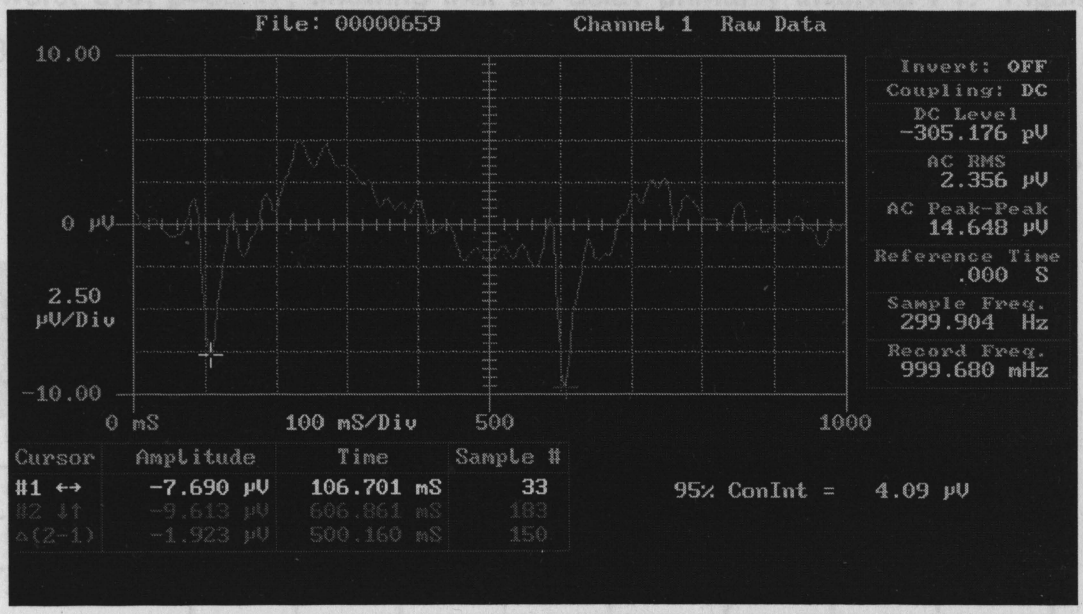
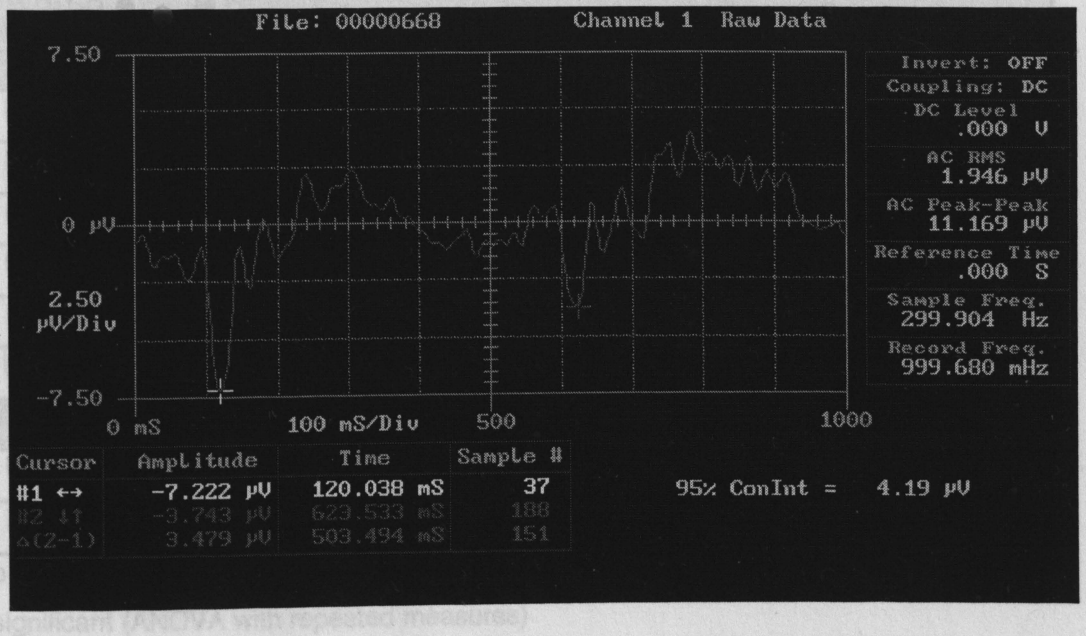


FIGURE 3.3 ***Example pattern VECP (27.5' check) of the other eye of the subject in Figure 3.2***

Result shows 2 traces, inverted by convention, and with the major positive peak (P1) marked. Note P1 is delayed to approximately 122 ms.



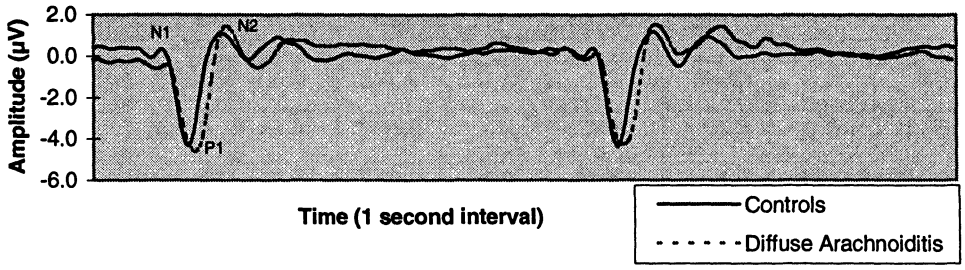
The large checkerboard results showed, on average, a 9 millisecond increase in latency of P1 for the diffuse arachnoiditis subjects (worst eye, p=0.001). There was no significant increase in the best eye results, indicating mainly a unilateral effect. The N1-P1 inter-peak latency increased (worst eye, p=0.047) showing that the delay primarily involved P1. Figure 3.4 shows the summary waveform and Table 3.9 lists the complete data.

TABLE 3.9 ***Average VECP latencies and amplitudes for each group to the large (55 min arc) checkerboard stimulus***

BEST EYE	Control (n=15)		Focal Arachnoiditis (n=3)			Diffuse Arachnoiditis (n=8)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
N1	81.6	9.3	81.8	2.6	NS	81.9	10.9	NS
P1	108.8	4.0	104.6	6.1	NS	114.0	10.0	NS
N2	146.4	9.5	139.0	6.2	NS	149.0	12.0	NS
N1-P1	27.2	8.4	22.9	4.3	NS	32.1	10.1	NS
P1-N2	37.6	10.8	34.4	4.2	NS	34.9	8.2	NS
N1-N2	64.8	14.9	57.2	4.9	NS	67.0	13.8	NS
Amplitude *(μV)*								
N1	-1.7	1.4	-2.4	1.1	NS	-1.1	0.9	NS
P1	5.7	3.1	6.3	2.6	NS	5.1	2.7	NS
WORST EYE	Control (n=15)		Focal (n=3)			Diffuse (n=8)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
N1	81.2	10.4	79.4	4.1	NS	84.1	8.9	NS
P1	108.8	4.5	102.9	4.8	NS	118.4	9.4	0.001
N2	145.3	9.9	138.3	6.4	NS	152.1	12.3	NS
N1-P1	27.6	9.7	23.5	3.7	NS	34.4	11.8	0.047
P1-N2	36.5	9.5	35.4	3.2	NS	33.6	7.6	NS
N1-N2	64.1	14.3	58.9	6.3	NS	68.0	13.5	NS
Amplitude *(μV)*								
N1	-2.0	1.7	-2.7	1.0	NS	-1.0	1.0	NS
P1	5.8	3.3	8.3	1.2	NS	4.4	2.3	NS

p values show significant difference from controls, significance level p<0.05, NS = not significant (ANOVA with repeated measures)

FIGURE 3.4 *GRAND AVERAGE WAVE*
Large check VECP for controls (n=30 eyes) and diffuse arachnoiditis (n=16 eyes)
2 waveforms are displayed in negative down convention.



With a small checkerboard stimulus, diffuse arachnoiditis patients showed a 9 millisecond increase in latency of P1 for diffuse arachnoiditis subjects (worst eye, p=0.001). In addition, there was a 4.5 millisecond increase in P1 latency for the best eye, indicating a potential bilateral, but not necessarily equal effect (best eye, p=0.050).

The grand average wave of the small checkerboard stimulus is shown in Figure 3.5 and the complete data is listed in Table 3.10.

FIGURE 3.5 *GRAND AVERAGE WAVE*
Small check VECP for controls (n=30 eyes) and diffuse arachnoiditis (n=16 eyes)
2 waveforms are displayed in negative down convention.
Note the increased latency of P1 and N2.

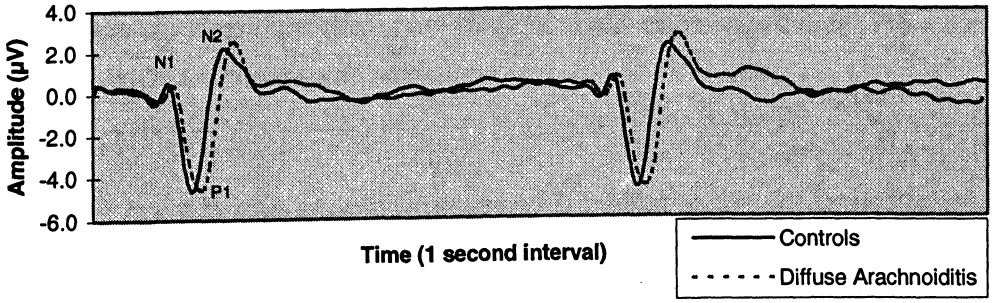


TABLE 3.10 ***Average VECP latencies and amplitudes of each group to the small checkerboard stimulus***

BEST EYE	Control (n=15)		Focal (n=3)			Diffuse (n=8)		
Latency*(ms)*	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
N1	83.7	7.2	84.4	3.2	NS	85.6	5.2	NS
P1	109.3	5.4	105.5	4.1	NS	115.2	9.0	0.050
N2	145.6	7.7	140.7	4.0	NS	153.7	12.0	0.037
N1-P1	25.5	6.9	21.2	2.0	NS	29.6	10.1	NS
P1-N2	36.3	8.3	35.2	2.3	NS	38.6	7.6	NS
N1-N2	61.9	10.3	56.3	2.5	NS	68.2	13.1	NS
Amplitude*(μV)*								
N1	-2.2	1.7	-3.1	1.2	NS	-1.4	1.1	NS
P1	6.1	2.9	9.0	1.2	NS	5.4	2.4	NS

WORST EYE	Control		Focal			Diffuse		
Latency*(ms)*	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
N1	83.4	9.2	84.4	4.7	NS	90.0	5.5	NS
P1	109.9	5.6	105.1	3.8	NS	119.4	8.2	0.001
N2	145.7	7.9	139.4	2.2	NS	154.9	12.4	0.013
N1-P1	26.5	8.9	20.7	2.2	NS	28.4	6.4	NS
P1-N2	35.8	9.0	34.3	1.9	NS	35.6	8.9	NS
N1-N2	62.3	12.5	55.0	3.1	NS	65.0	11.7	NS
Amplitude*(μV)*								
N1	-2.0	1.6	-3.6	1.0	NS	-1.4	1.0	NS
P1	6.0	3.4	9.4	1.1	NS	5.2	2.2	NS

p values show significant difference from controls, significance level $p<0.05$, NS = not significant (ANOVA with repeated measures)

The latency of N2 was also increased by 9 milliseconds for both the best and worst eyes (p=0.037 and 0.013 respectively). The fact that there was no significant increase of any inter-peak interval suggested that the whole waveform was delayed (Table 3.10).

The flash stimulus results showed a much larger variation within and between groups (Table 3.11). The only significant difference between groups was an increase in latency of N1 by 13 milliseconds for the diffuse arachnoiditis group (best eye, p=0.008). The grand average of waveforms shows that there is a reduction in amplitude of the early wavelets that precede N1.

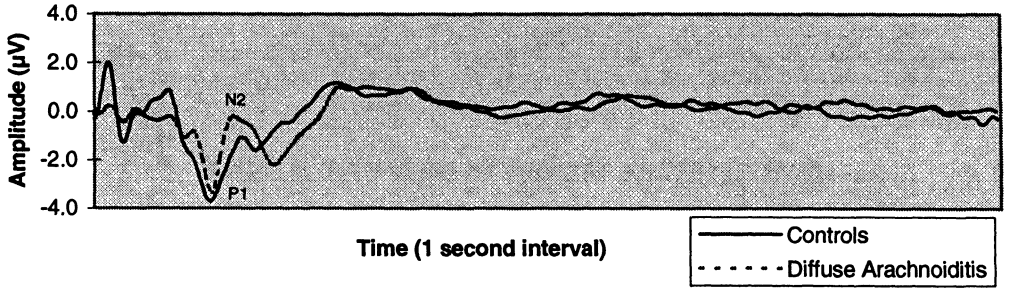
TABLE 3.11 ***Average flash VECP latencies and amplitudes by group***

BEST EYE	Control (n=15)		Focal (n=3)			Diffuse (n=8)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
N1	77.4	10.5	78.2	3.8	NS	91.0	11.7	0.008
P1	110.7	12.1	123.3	11.4	NS	116.2	13.9	NS
N2	153.3	17.2	152.3	11.9	NS	148.8	17.2	NS
N1-P1	29.7	23.9	45.2	9.8	NS	25.2	7.9	NS
P1-N2	42.2	26.8	28.9	10.5	NS	32.7	14.3	NS
N1-N2	71.9	28.4	74.1	13.5	NS	57.8	12.7	NS
Amplitude *(μV)*								
N1	-2.6	1.6	-2.0	0.8	NS	-2.0	1.3	NS
P1	5.5	3.4	7.3	1.9	NS	4.4	2.5	NS

WORST EYE	Control		Focal			Diffuse		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value	Mean	SD	*p*value
N1	78.6	11.1	77.6	5.3	NS	89.3	16.1	NS
P1	111.4	13.2	123.5	11.4	NS	118.7	17.0	NS
N2	154.1	18.0	153.6	14.6	NS	151.4	20.5	NS
N1-P1	29.1	23.6	29.5	28.4	NS	29.4	7.9	NS
P1-N2	41.8	26.9	18.3	6.8	NS	32.7	12.0	NS
N1-N2	70.9	28.1	47.8	34.2	NS	62.1	12.4	NS
Amplitude *(μV)*								
N1	-2.6	1.6	-2.0	0.6	NS	-2.2	1.8	NS
P1	5.2	2.8	7.1	1.3	NS	4.6	3.2	NS

p values show significant difference from controls, significance level $p<0.05$, NS = not significant (ANOVA with repeated measures)

FIGURE 3.6 ***GRAND AVERAGE WAVE***
Flash VECP for controls (n=30 eyes) and diffuse arachnoiditis (n=16 eyes)
1 waveform is displayed in negative down convention. Note the decrease in amplitude of P1 and the preceding wavelets for the arachnoiditis subjects.



Non-parametric statistics (Mann-Whitney U test of mean repeated measures) confirmed differences established with ANOVA.

For both checkerboard stimuli, there was a positive correlation between N1 latency and the existence of symptoms, and a negative correlation between P1 amplitude and symptoms (Table 3.12). There was no correlation however between the electrophysiology data and duration of disease.

TABLE 3.12 ***Correlation of VECP findings to existence of symptoms***

Variable	Eye	Correlation	p value
Large check N1 latency	Worst	0.609	0.047
Small check N1 latency	Worst	0.637	0.035
Flash N1 latency	Worst	0.693	0.018
Large P1 amplitude	Worst	-0.693	0.018
Small P1 amplitude	Worst	-0.635	0.036

Spearman's correlation (2-tailed), significance level $p<0.05$

3.2.3 Female VECP Results

To remove the effect of gender that was demonstrated in the control data, females from the control and diffuse arachnoiditis groups were also compared. There was no significant difference in age for these two groups (Table 3.13).

TABLE 3.13 ***Age of female subjects from the control and diffuse groups***

	Control n=6		Diffuse n=6		Significance Level*
	Mean	SD	Mean	SD	pvalue
Age (years)	52.7	15.0	59.2	6.8	0.485

*significance level $p<0.05$ (Mann Whitney U test)

For the larger checkerboard stimulus, the latencies for females only were similar to those already reported for males and females combined. There was almost a 9 millisecond increase in latency of P1 for diffuse arachnoiditis females compared to controls (worst eye, $p=0.020$).

In comparing the amplitude of the waveforms there was a significant reduction in the amplitude of P1 (worst eye, $p=0.048$) for diffuse arachnoiditis females and a 75% reduction of the size of N1 (worst eye, $p=0.008$) which is apparent in the grand average of the waveforms (Figure 3.7).

Again there was no significant difference for the best eye, indicating the effect was mainly unilateral (Table 3.14).

TABLE 3.14 ***Average VECP latencies and amplitudes of female controls and female diffuse subjects for the large (55 min arc) checkerboard stimulus***

BEST EYE	Controls (n=6)		Diffuse (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	83.6	8.6	84.2	11.5	NS
P1	110.7	3.4	116.6	9.7	NS
N2	149.6	6.9	152.1	8.6	NS
N1-P1	27.0	7.1	32.4	8.3	NS
P1-N2	38.9	8.1	33.3	3.0	NS
N1-N2	65.9	11.8	67.9	12.4	NS
Amplitude *(μV)*					
N1	-2.5	1.7	-1.0	0.9	NS
P1	7.5	3.4	5.6	2.4	NS

WORST EYE	Controls (n=6)		Diffuse (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	84.3	8.3	83.7	10.3	NS
P1	111.0	4.1	119.5	8.0	0.020
N2	149.1	6.9	156.0	9.2	NS
N1-P1	27.1	7.0	35.8	12.2	NS
P1-N2	37.7	7.0	36.5	7.1	NS
N1-N2	64.8	11.0	72.3	14.0	NS
Amplitude *(μV)*					
N1	-3.0	2.0	-0.8	0.7	0.008
P1	8.0	3.9	4.3	1.4	0.048

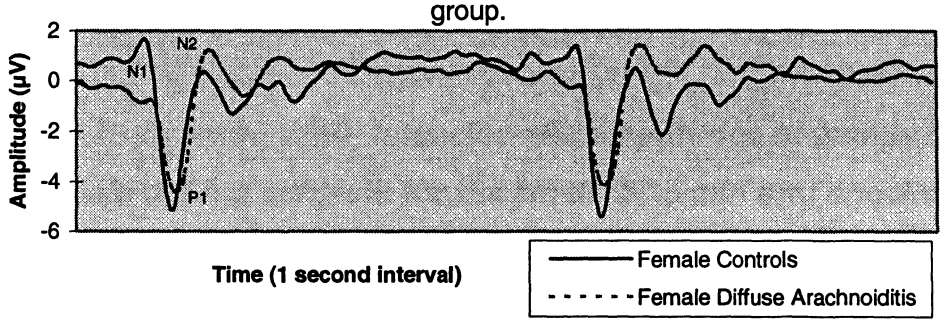
Significance level $p<0.05$, NS = not significant

(ANOVA with repeated measures)

FIGURE 3.7 *GRAND AVERAGE WAVE*

Large check VECP for female controls (n=12 eyes) and female diffuse arachnoiditis (n=12 eyes)

2 waveforms are displayed in negative down convention. Note the reduction in amplitude of N1 and P1 for the arachnoiditis group.

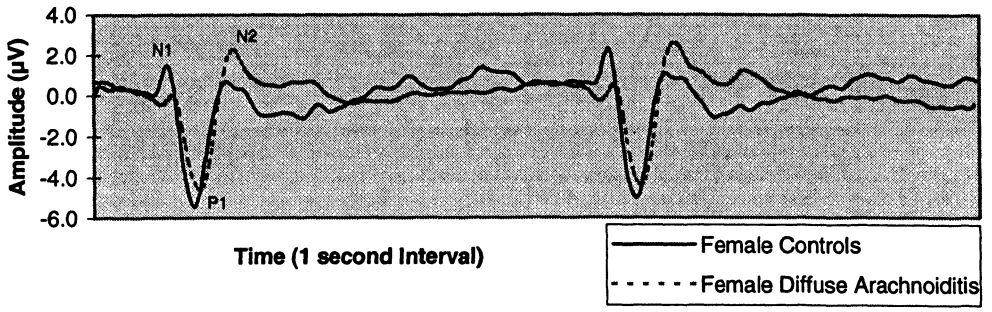


For the small checkerboard stimulus, as in the combined male and female results, both P1 and N2 showed increased latencies for the diffuse arachnoiditis females compared to control females (Table 3.15). P1 was increased by almost 9 milliseconds for the worst eye (p=0.003) and N2 was increased by 11 milliseconds for both eyes (p=0.009 and 0.001 for best and worst eyes respectively). The increase in the N1-N2 inter-peak interval (best eye, p=0.045) showed that the majority of the waveform was delayed.

FIGURE 3.8 *GRAND AVERAGE WAVE*

Small Check VECP for Female Controls (n=12 eyes) and Female Diffuse Arachnoiditis (n=12 eyes)

2 waveforms are displayed in negative down convention.Note the reduction in amplitude of N1and P1 for the arachnoiditis group.



The small checkerboard results were similar to the large check results in that the amplitude of N1 for female diffuse arachnoiditis subjects was less than half that of female controls (best eye, p=0.042). This is shown in the grand average waveforms along with an increase in amplitude of N2 (Figure 3.8).

TABLE 3.15 ***Average VECP latencies and amplitudes of female controls and female diffuse subjects for the small (27.5 min arc) checkerboard stimulus***

BEST EYE	Controls (n=6)		Diffuse (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	85.2	7.8	86.0	6.0	NS
P1	111.6	5.6	118.0	7.7	NS
N2	147.2	8.5	158.8	8.4	0.009
N1-P1	26.4	6.6	32.0	9.8	NS
P1-N2	35.6	9.2	40.8	7.0	NS
N1-N2	62.0	10.0	72.8	11.2	0.045
Amplitude *(μV)*					
N1	-3.0	2.3	-1.1	0.9	0.042
P1	7.6	3.5	5.6	2.0	NS

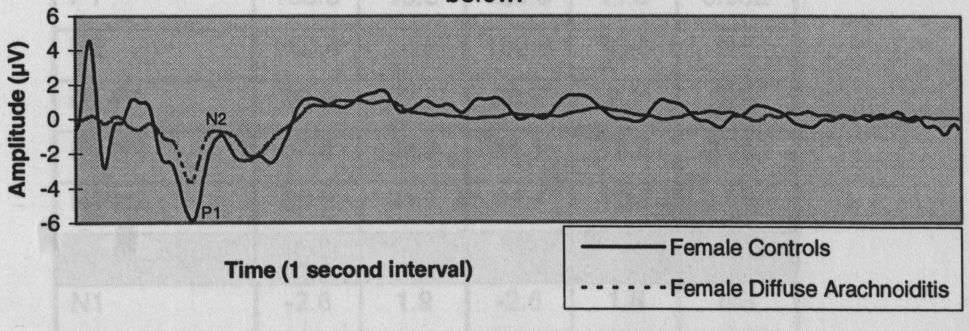
WORST EYE	Controls (n=6)		Diffuse (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	87.5	7.6	91.4	4.9	NS
P1	112.2	5.4	120.8	6.1	0.003
N2	147.3	6.2	158.1	8.4	0.001
N1-P1	24.7	6.2	29.4	6.2	NS
P1-N2	35.0	8.0	37.3	9.2	NS
N1-N2	59.7	9.6	66.7	10.6	NS
Amplitude *(μV)*					
N1	2.8	2.0	1.2	0.8	NS
P1	7.3	4.1	5.3	1.8	NS

Significance level p<0.05, NS = not significant
(ANOVA with repeated measures)

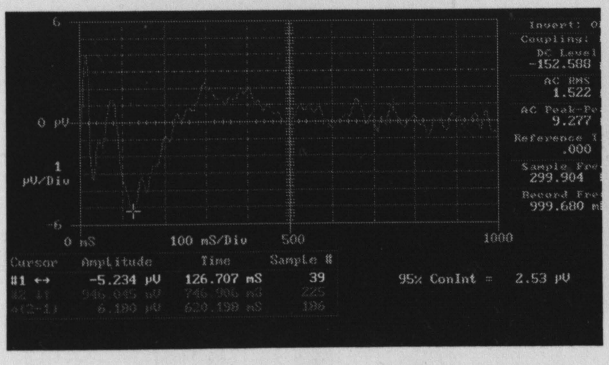
The female-only results with the flash stimulus showed a greater difference between groups compared to the combined gender results (Table 3.16). For the female diffuse arachnoiditis group, N1 was increased by 23 milliseconds bilaterally (p=0.002 and p=0.010 for best eye and worst eye respectively) and P1 was increased by 17 milliseconds in the worst eye only (p=0.032). For both eyes the inter-peak intervals showed the P1-N2 interval was abnormally condensed (p=0.028 and p=0.045 for best eye and worst eye respectively).

The average waveform of the female flash results also showed a reduction in amplitude of the early wavelets for the diffuse subjects (Figure 3.9).

FIGURE 3.9 ***GRAND AVERAGE WAVE***
Flash VECP for female controls (n=30 eyes) and female diffuse arachnoiditis (n=16 eyes)
Waveforms are in negative down convention. P1 and early wavelets are reduced for the arachnoiditis subjects. See also inset below.



INSET Two different female control results are shown below to show that the amplitude of the early wavelets in the control grand average is not an artefact of jitter.



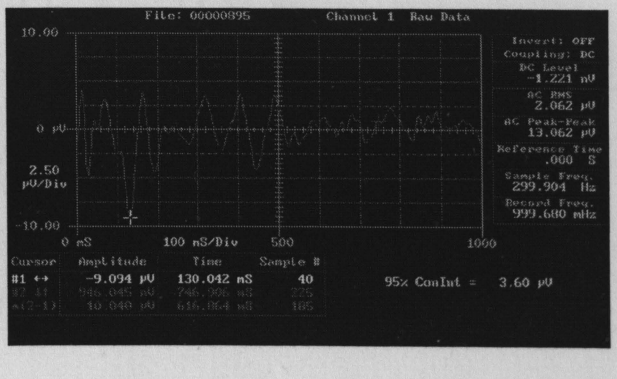


TABLE 3.16 ***Average VECP latencies and amplitudes of female controls and female diffuse subjects for the flash stimulus***

BEST EYE	Controls (n=6)		Diffuse (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	71.8	10.3	94.7	9.6	0.002
P1	107.8	14.1	123.9	7.7	NS
N2	161.3	14.9	153.9	12.6	NS
N1-P1	33.2	29.7	29.3	6.0	NS
P1-N2	56.3	32.6	30.0	11.6	0.028
N1-N2	89.5	21.6	59.3	11.9	0.011
Amplitude *(μV)*					
N1	-2.9	2.0	-2.0	0.9	NS
P1	6.3	4.2	5.2	2.0	NS

WORST EYE	Controls (n=6)		Diffuse (n=6)		
Latency *(ms)*	Mean	SD	Mean	SD	*p*value
N1	72.4	10.5	95.8	13.9	0.010
P1	108.0	15.6	125.5	11.8	0.032
N2	160.4	14.6	160.6	13.6	NS
N1-P1	30.4	29.5	29.7	9.1	NS
P1-N2	57.6	32.1	35.1	13.2	0.045
N1-N2	88.0	21.7	64.8	12.2	0.044
Amplitude *(μV)*					
N1	-2.6	1.9	-2.6	1.8	NS
P1	5.4	3.2	5.5	3.2	NS

Significance level $p<0.05$, NS = not significant

(ANOVA with repeated measures)

3.3 Visual Reaction Time Results

3.3.1 Controls

Analysis of control data showed no significant differences between repeated measures for visual reaction time (Appendix 1.8). This justified using the visual reaction time (VRT) mean for comparison of male and female results.

There was no gender difference for the single fastest visual reaction time (FVRT), however males did have a faster average (VRT) than females (worst eye, p=0.026).

TABLE 3.17 ***Visual reaction time (VRT) and single fastest visual reaction time (FVRT) for the control group***

BEST EYE	Males (n=9)		Females (n=6)		
	Mean	SD	Mean	SD	pvalue
VRT *(ms)*	245.5	46.4	285.7	50.0	NS
FVRT *(ms)*	213.1	34.6	243.6	34.9	NS

WORST EYE	Males (n=9)		Females (n=6)		
	Mean	SD	Mean	SD	pvalue
VRT *(ms)*	241.3	39.4	284.8	50.9	0.026
FVRT *(ms)*	208.8	29.2	245.5	52.6	NS

Significance level p<0.05, NS = not significant (Mann-Whitney U)

3.3.2 Test Groups

There were statistically significant differences between repeated measures of individual test subjects (Appendix 1.8). Therefore comparisons between test groups and controls were made using ANOVA with repeated measures.

There were no differences between the focal arachnoiditis and control groups. The diffuse arachnoiditis subjects had average visual reaction times that were at least 90 milliseconds or 34% slower than controls (p=0.004 and 0.003 for best eye and worst eye respectively). The difference between diffuse arachnoiditis and control subjects for the single fastest visual reaction time was not significant.

TABLE 3.18 ***Visual reaction time (VRT) and single fastest visual reaction time (FVRT) for each group***

BEST EYE	Control (n=15)		Focal (n=3)			Diffuse (n=8)		
	Mean	SD	Mean	SD	pvalue	Mean	SD	pvalue
VRT *(ms)*	253.9	49.3	250.7	35.8	NS	343.6	113.5	0.004
FVRT *(ms)*	216.8	40.3	213.6	30.4	NS	262.8	49.9	NS

WORST EYE	Control		Focal			Diffuse		
	Mean	SD	Mean	SD	pvalue	Mean	SD	pvalue
VRT *(ms)*	266.3	50.8	269.0	56.4	NS	363.2	111.4	0.003
FVRT *(ms)*	232.0	37.8	205.9	25.7	NS	290.7	71.9	NS

p values show significant difference from controls, significance level $p<0.05$, NS = not significant (VRT:ANOVA with repeated measures, FVRT: Mann-Whitney U)

Non-parametric tests confirmed the same differences (Appendix 1.8).

There was no correlation between either mean visual reaction time or fastest visual reaction time and symptoms or duration of disease.

3.3.3 Female Visual Reaction Time

Due to the gender difference demonstrated in the control data, female-only results were also compared using ANOVA with repeated measures (Table

3.19). The average reaction times for the diffuse arachnoiditis females were delayed to the same extent as in the combined gender data (p=0.013 and 0.014 for best eye and worst eye respectively). The single fastest visual reaction time was also delayed with a 27% increase in latency compared to controls (worst eye, p=0.041). Non-parametric tests confirmed the same differences.

TABLE 3.19 ***Mean visual reaction time (VRT) and single fastest visual reaction time (FVRT) of female controls and diffuse female subjects***

BEST EYE	Control (n=6)		Diffuse (n=6)		
	Mean	SD	Mean	SD	pvalue
VRT *(ms)*	275.8	52.4	386.9	105.3	0.013
FVRT *(ms)*	234.8	49.3	285.3	32.2	NS

WORST EYE	Control (n=6)		Diffuse (n=6)		
	Mean	SD	Mean	SD	pvalue
VRT *(ms)*	294.7	46.4	392.5	101.2	0.014
FVRT *(ms)*	254.3	36.4	322.5	48.6	0.041

Significance level $p<0.05$, NS = not significant

(VRT: ANOVA with repeated measures, FVRT Mann-Whitney U test)

CHAPTER 4: DISCUSSION

As expected, the results of the present study confirm that the visual system of arachnoiditis patients is significantly different to that of neurologically normal controls. The findings of this study agree with those of the isolated case report by Wong where a patient developed increased VECP latencies with normal visual acuity long after iophendylate myelography.[61] For Wong's patient and the subjects reported in the current study, the visual involvement is similar to that of multiple sclerosis except that visual effects are related to the encroachment of arachnoiditis in the brain rather than to the duration of disease.

4.1 Increased Latency of the VECP

The most profound visual sign of arachnoiditis is the increase in latency of the visual evoked potential. The P1 is significantly delayed for large checks, small checks and flash stimuli. This agrees with the findings of others who have found that although N1, P1 and N2 can all be affected in optic nerve dysfunction, a delay in P1 is the most common.[166,167,169] It is not impossible however for N1 and N2 to be abnormal while P1 remains unaffected[183] and it must also be remembered that P1 is more susceptible than N1 to the influences of age, sex and stimulus.[184]

The diffuse arachnoiditis group also shows a delay of N2 to small checks, which is not commonly reported in optic neuritis, but has been demonstrated in subjects exposed to lead[185] which is known to cause arachnoiditis. Likewise, organic solvents have been linked to arachnoiditis with an increased latency of the VECP.[186] In contrast, patients with Parkinson's disease, which is not known to involve demyelination,[187] have a significant delay of the N2 component only.[188]

4.2 Reduced Amplitude of the VECP

Although latency is a more sensitive indicator that amplitude, the assessment of amplitude in this study is particularly important because of the possibility of a toxic neuropathy in which case an amplitude reduction might be the only abnormality.[189]

In the arachnoiditis subjects there is a significant reduction of P1 amplitude for large checks and a reduction of N1 amplitude for both check sizes. The reduction of N1 to large checks is more significant than that to small checks. The constellation of the delayed P1, the greater reduction in amplitude to large checks and the decrease in contrast sensitivity to large spatial frequencies, is suggestive of a magnocellular pathway deficit.[190] N1 is thought to represent a mainly foveal, contrast dependent component whereas P1 probably also represents luminance parafoveal processing.[191] Such a selective damage to the magnocellular pathway might explain why the N1 latency to pattern stimuli is normal and why colour vision appears preserved.

If such a preferential impairment is true, then a low contrast stimulus flickering at a fast rate would be a more sensitive test.[190] The use of low contrast stimuli has proven to be no more sensitive in detecting optic nerve involvement[192] but Regan[161] has shown an increased sensitivity of a flicker stimulus. Using a medium to fast rate (13-25Hz) he was able to demonstrate visual dysfunction in subjects who had spinal multiple sclerosis but a normal pattern VECP. The flicker VECP showed an abnormal increase in latency, and if visual acuity was reduced, there was also a reduction in the amplitude.

4.3 Increased Latency of the Flash VECP

Compared to pattern stimuli, the flash VECP showed the largest variation and the longest delay (female result). But in optic neuritis the flash latencies are usually only greater than pattern latencies during the acute phase.[163] In bacterial meningitis, however, the amplitude of the flash is reduced initially and latency is increased in the later stages of the disease.[17] It could be that because the flash VECP is derived from the peripheral retina, it represents the potentially impaired magnocellular pathway.[163] Flash VECPs are also more delayed than checkerboard recordings in Alzheimer patients[193] which is also thought to involve a magnocellular deficit.[190]

The disappearance of the early wavelets in the arachnoiditis subjects might be explained by the fact that only very bright flash stimuli elicit these wavelets.[150] They usually begin between ten and 25 milliseconds and are believed to originate somewhere in the fibre tracts. Their absence in the arachnoiditis subjects helps eliminate the possibility of retinal or cortical lesions causing the visual effects.

4.4 Significance of Abnormal VECP

Although an abnormal VECP is not diagnostic of any particular disease, the type of change to the VECP provides some information about the underlying disease process. If amplitude is affected more than latency it is often indicative of axonal degeneration, such as in Freidrich's ataxia, but when latency is more affected, as it is for the arachnoiditis group, it is most likely demyelinating disease.[163] The average increase in latency is greater than that found in asymptomatic AIDS patients[114] but not as great as that reported in acute optic neuritis.[163] This is consistent, as the arachnoiditis patients are

not necessarily in an acute phase of disease. However, like MS[194] the arachnoiditis subjects show no correlation between the VECP changes and duration or progression of disease. It may be that arachnoiditis subjects also go through periods of remission and exacerbation during fluctuations in the status of inflammation.

The two subjects with balance problems had monocular delays which can cause a loss in depth perception related to the Pulfrich phenomenon.[195] This effect is highly correlated to optic nerve conduction deficits[196] and may explain why neither patient was confident to drive. Measurement and neutralisation of the Pulfrich phenomenon with neutral density filters may have offered relief to these symptomatic patients.

Unrelated to the arachnoiditis, the VECP abnormalities could be secondary to depression. Recent research has shown an increase in the latency of flash VECP of P1 and N2 in patients with a cognitive impairment due to depression.[197] Arachnoiditis patients are not generally drug free so it is also possible that the changes are caused by the pharmacological effect of medications. Drug effects however mainly affect the VECP amplitude and are usually symmetrically bilateral.[189] Comparison of the arachnoiditis group to another debilitated group with a similar medication profile may have helped clarify this point.

It is also possible, that in such an emotional disease, test subjects intentionally blurred the stimulus but the amount of over accommodation required[150] to cause the delay recorded would have been difficult to maintain. Nevertheless, a cycloplegic with suitable refraction may have been more suitable.

4.5 Implication of Clinical Findings

If the visual effect is a low grade optic neuritis, then the other clinical findings of reduced vision in the symptomatic eye, reduced contrast sensitivity, afferent pupil defect, optic disc pallor and an isolated third nerve palsy, are not at all surprising. Symptoms, which included intermittent blurring or blacking out of vision, were correlated to increased latency of N1 for all stimuli and reduced amplitude of P1 for both checks, which fits with Cuyper's claim that N1 latency is a more sensitive indicator than P1 latency of optic nerve dysfunction. The reports of pain in and around the eye could be related to optic nerve inflammation as the meningeal sheaths are innervated by sensory nerve fibres.[14] For the arachnoiditis patients who were symptom free, optic nerve involvement is still possible, as there are patients with optic neuritis who do not experience clear clinical symptoms.[198]

Pupils were not often involved which is consistent with the other clinical findings of the study as a relative afferent pupillary defect is usually proportional to the amount of visual loss.[199] The infrequency of pupil involvement suggests either low grade involvement or fairly bilateral disease.[200] A more sensitive test might have been to measure direct and indirect pupillary light latency which has been shown to be delayed in multiple sclerosis.[173]

For most of the arachnoiditis subjects high and low contrast acuities were normal and contrast sensitivity to low spatial frequencies was reduced. This is consistent with the findings of the Optic Neuritis Trial where Pelli-Robson contrast sensitivity was more sensitive than visual fields (Humphrey Field Analyser mean deviation score) and colour vision (Farnsworth-Munsell 100-hue) in detecting visual dysfunction.[159] Visual pathways are frequently involved in multiple sclerosis but visual field defects are infrequently reported due to the inadequacies of perimetry.[201]

The Optic Neuritis Study[159] has shown that at 6 months after optic neuritis in eyes where visual acuity has returned to normal, almost half will still have reduced contrast sensitivity but only 25% will have abnormal colour vision. This shows that in an eye that is recovering from optic neuritis, the key is to measure "non fixational" visual function tests that test the magnocellular rather than the parvocellular system. In comparison, when the optic neuritis is acute, contrast sensitvity is affected in almost all patients and visual acuity is also usually affected.[159]

The preservation of visual acuity and contrast sensitivity to high spatial frequencies in the arachnoiditis group is consistent with the preservation of the small check P1 amplitude. If contrast sensitivity had been reduced at all spatial frequencies then amplitude of both the large and small check responses would have been reduced.[171] Acuity is a measurement of only one point on the contrast sensitivity curve and is dependent more on the number of fibres in conduction rather than the speed of conduction.[170]

The difference between the arachnoiditis subjects in this study and patients who have definite optic neuritis may therefore be revealed in comparing the entire contrast sensitivity function. While optic neuritis is known to affect a wide range of spatial frequencies,[159] results from the current study suggest that in arachnoiditis, the low to medium spatial frequencies, as detected by the Pelli-Robson test, are more likely to be affected. Such a notching or loss of one part of the contrast sensitvity curve may help explain those arachnoiditis patients who had normal visual acuity but still complained of blurred vision. Likewise it might also explain why many of the arachnoiditis patients described such vague visual symptoms.

For the patient with third nerve abnormalities, although sixth nerve damage is more common in CNS disease[124,127] the third nerve can be damaged in the subarachnoid space by meningitis.[202] There may have been some aberrant

reinnervation of the levator palpebral muscle from the third nerve fibres of the extraocular muscles, as the ptosis was most dramatic during adduction when only the sixth nerve was employed.[203] For this isolated case, there may have been many other unrelated causes of the palsy.

4.6 Implication of VRT Result

The VRT measurement of this study was designed to measure simple reaction time which is primarily dependent on sensory processing and motor speed.[203] Females were slower than males, and with sex controlled, diffuse arachnoiditis subjects were almost 100 milliseconds slower than controls. In multiple sclerosis the VRT is delayed according to duration of disease at five milliseconds per year[176,177] but there was no correlation in the arachnoiditis group. Because of the multifactorial aetiology of arachnoiditis, no two individuals progress at the same rate.[8]

Since the subject does not know when the stimulus will come, this measure of VRT also includes a degree of sustained attention.[204] Some of this effect is removed by comparing the fastest VRT[175] in which case the arachnoiditis subjects were not as significantly delayed. This means that the simple VRT result is showing the effect of an impaired cognitive component in addition to the sensory-motor loss. Such an impairment may also reduce the VECP amplitude as it too is influenced by the subject's level of attention.[205] Just as multiple sclerosis can produce a "subcortical dementia"[178] there may also be a similar cognitive deficit in arachnoiditis.

It is also known, however, that tiredness can almost double VRT in normal subjects,[206] so tiredness alone, which was frequently reported by the arachnoiditis group, may have caused the recorded delay. Performing the

VRT measurements at the beginning, instead of at the end of the examination, may have helped to clarify this point.

4.7 Proposed Aetiology of Visual Effects

From the evidence presented so far, although speculative, it is probable that the visual effects found are due to a demyelinating process but what could cause such a demyelination is less clear.

The current study involved patients who developed arachnoiditis following exposure to the contrast agent, iophendylate. The visual deficit therefore may be a toxic effect. Intrathecal gold, for instance, which is used to treat medulloblastoma, is known to pool in the basal cisterns and caudal sac, delivering a very inhomogenous dose and often resulting in arachnoiditis.[207] However in toxic neuropathy vision loss is painless and symmetrically bilateral. Most drug-induced neuropathies are axonal affecting only the amplitude of the VECP and producing subtle temporal pallor of the optic disc with a clear nerve fibre layer defect in the papillomacular bundle.[167] The only known drug-induced neuropathies that are demyelinating are perhexiline and amiodarone.[208] It seems that iophendylate is not neurotoxic but its continued presence in the subarachnoid space is known to cause chronic irritation.[209] It is probably the ensuing arachnoiditis more than the drug itself that ultimately affects vision.

Such is the process in opto-chiasmatic arachnoiditis where the thickened arachnoid tissue forms adhesions that compress and directly invade visual fibres.[15] In opto-chiasmatic arachnoiditis, as in the present study, headaches precede visual symptoms, there is a lack of achromatopsia, there is hyperemia or pallor of the disc and an occasional third or sixth nerve palsy.[15] Arachnoidal reaction to retained iophendylate is particularly prominent

around the brain stem[210] which may be enough to cause compression of the optic nerve. But in diseases that directly compress the nerve, such as Graves disease, only VECP amplitude is reduced[211] and there are changes to the waveform shape.[212] Latency may be affected later in the disease but there is also retro-degeneration that eventually causes abnormalities in the ERG.[211] It is unlikely, therefore, that the effect shown in the current study is due to compression alone.

From the comparisons already drawn to multiple sclerosis it is more likely that the process in the arachnoiditis subjects is also of an inflammatory nature, not unlike the inflammatory reaction that is well known to occur in the lumbar spine. In both multiple sclerosis and lumbar arachnoiditis there is a mononuclear cell infiltration of the nerve and an invasion of macrophages to remove the myelin.[213] As in optic neuritis, oedema probably causes the reduction in amplitude of the VECP and the increase in latency is most likely related to the length of the demyelination.[172] A demyelinated length of about one centimetre would cause the 5-10 millisecond delay recorded in the arachnoiditis subjects[214] and might even be visible on MRI.

One CT report from a patient in the present study did show an enlarged optic nerve in the eye with the delayed VECP, however head tilt alone could have caused such an appearance (see Appendix 1.9). Other patients showed reports that referred to "retained Myodil droplets in the subarachnoid space" but none specifically reported plaques. Two of the male diffuse arachnoiditis patients had previously been diagnosed as suffering multiple sclerosis which was later confirmed as arachnoiditis.

Why only some patients who undergo myelography develop arachnoiditis may be explained by the same genetic and environmental factors that play a role in the development of multiple sclerosis.[155] Some evidence to support this includes the increased incidence of arachnoiditis from the drug

trimethoprim-sulfamethoxazole in women with underlying auto-immune or collagen vascular disorders.[215] It has also been suggested that there are antigens to iophendylate in the arachnoid membrane.[2] Maybe the contrast agent precipitates an autoimmune process that attacks the myelin sheath.

The underlying process causing the visual effects of this study, although like multiple sclerosis, are most likely a combination of the ideas already discussed. Iophendylate that enters the cranium can potentially pool in the basal cisterns and it is known to irritate the delicate arachnoid tissue. The subsequent development of local arachnoiditis could strangle nerves within the visual pathway, causing ischemia and eventually demyelination.

The magnocellular pathway deficit could then be purely related to the more vulnerable anatomical position of magnocellular axons in the posterior pathway. Genetic factors may play a role in determining who responds and the level of response, however dose and history of previous inflammation can not be ignored.

4.8 Future Research

Better understanding of the visual loss and underlying process could be gained by computerised perimetry and cerebral MRI. T2 weighted fast spin echo imaging offers an adequate view of the optic nerve and subarachnoid space without being invasive.[39] Just as electrophysiology has been used in AIDS patients, examination of the VECP over time would certainly give these often neglected patients some method of monitoring the progression of the disease.

With limited treatment options, prevention is far better than cure and the question should be asked as to what are the potential long term side effects

of the current dyes. Intrathecal methotrexate for instance, which has been reported to cause acute effects, can result in chronic symptoms following irradiation.[216]

The situation is also complicated by the fact that acute arachnoiditis can become chronic many years later in life.[6] An understanding of how the chronic disease relates to acute chemical reactions might help at least predict which patients are at risk of chronic disease.

CHAPTER 5: CONCLUDING DISCUSSION

While routine ophthalmological or neurological examination does not typically reveal visual involvement in arachnoiditis, more sensitive tests have shown that it can lead to chronic visual involvement not unlike the low grade optic neuritis seen in multiple sclerosis. If there is involvement of the arachnoiditis in the central nervous system, there is an increased likelihood of visual signs and symptoms.

It is suspected that changes to the VECP in the acute phase of arachnoiditis are oedema related, whereas the chronic effects described in this study are probably related to demyelination. For the VECP to be affected, there must be involvement of the central nervous system beyond the lumbar spine which, for these patients, has much greater significance than the potential threat to vision.

Electrophysiology therefore offers a suitable test to not only detect CNS toxicity of contrast agents, but when arachnoiditis develops, it can evaluate progression of the disease and also the benefits of treatment.

Although most countries now recognise a relationship between contrast agents and acute arachnoiditis, the full extent of the chronic disease is only beginning to unfold. There are still many individuals living with iophendylate arachnoiditis who have a vested interested in understanding the full effects that can occur when the entire CNS can be involved.

Further research would clarify what happens to vision over time, but it might be more prudent to investigate the visual system of patients who have a history of nonionic water based myelography, so that some action can be taken if deemed to be necessary.

This research however has demonstrated that chronic adhesive arachnoiditis secondary to iophendylate myelography can affect vision. This effect is not always symptomatic and is related to the extent of arachnoiditis in the brain. In practical terms it has been demonstrated that patients with visual involvement have reduced contrast sensitivity and reduced visual reaction time. The progression of visual effects is unknown, but the understanding that there can be a wider CNS involvement in chemical arachnoiditis may help push the trend towards the use of less invasive radiological techniques.

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APPENDIX 1: STATISTICAL ANALYSES

APPENDIX 1.1 Between group analysis of sex and age

SEX * GROUP Chi-Square Tests

	Value	df	Asymp. Sig (2-sided)	Exact Sig. (2-sided)	Exact Sig (1-sided)	Point Probability
Pearson Chi-Square	2.933[a]	2	.231	.371		
Likelihood Ratio	3.037	2	.219	.371		
Fisher's Exact Test	2.886			.371		
Linear-by-Linear Association	2.231[b]	1	.135	.199	.100	.057
N of Valid Cases	26					

a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is 1.50
b. The standardised statistic is 1.494

AGE * GROUP Test Statistic[b,c]

			AGE
Chi-Square			.832
df			2
Asymp. Sig.			.660
Monte Carlo Sig.	Sig.		.674[a]
	99% Confidence Interval	Lower Bound	.662
		Upper Bound	.686

a. Based on 10000 sampled tables with starting seed 2000000
b. Kruskal Wallis Test
c. Grouping Variable: GROUP

APPENDIX 1.2 Between group analysis of disease duration

FOCAL * GROUP for Disease Duration Test Statistic[b]

	DURATION
Mann-Whitney U	9.500
Wilcoxon W	45.500
Z	-.516
Asymp. Sig. (2-tailed)	.606
Exact Sig. [2*(1-tailed Sig.)]	.630[a]
Exact Sig. (2-tailed)	.667
Exact Sig. (1-tailed)	.339
Point Probability	.048

a. Not corrected for ties.
b. Grouping Variable: GROUP

APPENDIX 1.3 Between group analysis of visual acuity (VA), low contrast visual acuity (LCVA) & contrast sensitivity (CS)

VA, LCVA & CS* GROUP Test Statistic[b,c]

				VA	LCVA	PELLI
Best	Chi-Square			.666	2.029	4.400
	df			2	2	2
	Asymp. Sig.			.717	.363	.111
	Monte Carlo Sig.	Sig.		.737[a]	.384[a]	.120[a]
		99% Confidence Interval	Lower Bound	.726	.371	.112
			Upper Bound	.748	.396	.128
Worst	Chi-Square			4.947	3.389	6.312
	df			2	2	2
	Asymp. Sig.			.084	.184	.043
	Monte Carlo Sig.	Sig.		.080[a]	.189[a]	.034[a]
		99% Confidence Interval	Lower Bound	.073	.179	.029
			Upper Bound	.087	.199	.039

a. Based on 10000 sampled tables with starting seed 299883525
b. Kruskal Wallis Test
c. Grouping Variable: GROUP

CS for CONTROL vs DIFFUSE Test Statistic[b]

	DURATION	
	Best PELLI	Worst PELLI
Mann-Whitney U	32.500	23.000
Wilcoxon W	68.500	59.000
Z	-1.891	-2.526
Asymp. Sig. (2-tailed)	.059	.012
Exact Sig. [2*(1-tailed Sig.)]	.076[a]	.016[a]
Exact Sig. (2-tailed)	.047	.011
Exact Sig. (1-tailed)	.028	.004
Point Probability	.004	.001

a. Not corrected for ties. Bonferroni correction applied.
b. Grouping Variable: GROUP

CS for NON SYMPTOMATIC EYE vs SYMPTOMATIC EYE Test Statistic[b]

	VA	LCVA	PELLI
Mann-Whitney U	26.000	51.000	43.000
Wilcoxon W	104.000	129.000	98.000
Z	-2.278	-.601	-1.241
Asymp. Sig. (2-tailed)	.023	.548	.215
Exact Sig. [2*(1-tailed Sig.)]	.025[a]	.582[a]	.283[a]
Exact Sig. (2-tailed)	.021	.565	.354
Exact Sig. (1-tailed)	.011	.282	.177
Point Probability	.001	.010	.118

a. Not corrected for ties
b. Grouping Variable: SYM

DISEASE DURATION * VA, LCVA & CS Correlation

			DURATION		
			Correlation Coefficient	Sig. (2-tailed)	N
Best	Spearman's rho	VA	.191	.573	11
		LCVA	-.137	.687	11
		CS	.076	.824	11
Worst	Spearman's rho	VA	.059	.864	11
		LCVA	-.178	.600	11
		CS	-.150	.660	11

APPENDIX 1.4 Between group analysis of colour vision

C Index and S Index for FOCAL vs CONTROL Test Statistic[b]

	Best		Worst	
	C Index	S Index	C Index	S Index
Mann-Whitney U	22.000	14.500	15.000	19.000
Wilcoxon W	142.00	134.50	135.00	25.000
Z	-.062	-.984	-.916	-.422
Asymp. Sig. (2-tailed)	.951	.325	.360	.673
Exact Sig. [2*(1-tailed Sig.)]	1.000[a]	.360[a]	.426[a]	.738[a]
Exact Sig. (2-tailed)	1.000	.419	.426	.727
Exact Sig. (1-tailed)	.502	.205	.200	.380
Point Probability	.043	.049	.027	.029

a. Not corrected for ties
b. Grouping Variable: GROUP

C Index and S Index for DIFFUSE vs CONTROL Test Statistic[b]

	Best		Worst	
	C Index	S Index	C Index	S Index
Mann-Whitney U	53.500	59.500	40.500	42.500
Wilcoxon W	173.50	95.500	160.50	162.50
Z	-.435	-.034	-1.296	-1.147
Asymp. Sig. (2-tailed)	.663	.973	.195	.251
Exact Sig. [2*(1-tailed Sig.)]	.681[a]	.975[a]	.213[a]	.265[a]
Exact Sig. (2-tailed)	.685	.983	.212	.264
Exact Sig. (1-tailed)	.342	.489	.103	.134
Point Probability	.014	.017	.003	.009

a. Not corrected for ties
b. Grouping Variable: GROUP

APPENDIX 1.5 Analysis of repeat measurements for male and female control subjects

CONTROL Large N1 Latency Test Statistic[a]

Large N1 Latency				Male	Female
Best	N			9	6
	Chi-Square			8.596	8.446
	df			5	5
	Asymp. Sig.			.126	.133
	Monte Carlo Sig.	Sig.		.128	.125
		99% Confidence Interval	Lower Bound	.120	.116
			Upper Bound	.137	.133
Worst	N			9	6
	Chi-Square			9.214	17.362
	df			5	5
	Asymp. Sig.			.101	.004
	Monte Carlo Sig.	Sig.		.099	.001
		99% Confidence Interval	Lower Bound	.091	.000
			Upper Bound	.107	.001

a. Friedman Test

CONTROL Large P1 Latency Test Statistic[a]

Large P1 Latency				Male	Female
Best	N			9	6
	Chi-Square			7.355	7.342
	df			5	5
	Asymp. Sig.			.196	.196
	Monte Carlo Sig.	Sig.		.190	.190
		99% Confidence Interval	Lower Bound	.179	.179
			Upper Bound	.200	.200
Worst	N			9	6
	Chi-Square			7.894	10.231
	df			5	5
	Asymp. Sig.			.162	.069
	Monte Carlo Sig.	Sig.		.153	.055
		99% Confidence Interval	Lower Bound	.144	.049
			Upper Bound	.162	.061

a. Friedman Test

CONTROL Large N2 Latency Test Statistic[a]

Large N2 Latency				Male	Female
Best	N			9	6
	Chi-Square			6.027	3.398
	df			5	5
	Asymp. Sig.			.304	.639
	Monte Carlo Sig.	Sig.		.311	.660
		99% Confidence Interval	Lower Bound	.299	.648
			Upper Bound	.323	.672
Worst	N			9	6
	Chi-Square			10.217	4.950
	df			5	5
	Asymp. Sig.			.069	.422
	Monte Carlo Sig.	Sig.		.059	.439
		99% Confidence Interval	Lower Bound	.053	.426
			Upper Bound	.065	.451

a. Friedman Test

CONTROL Large N-P Interval Test Statistic[a]

Large N-P Interval				Male	Female
Best	N			9	6
	Chi-Square			2.755	3.086
	df			5	5
	Asymp. Sig.			.738	.687
	Monte Carlo Sig.	Sig.		.762	.715
		99% Confidence Interval	Lower Bound	.751	.704
			Upper Bound	.773	.727
Worst	N			9	6
	Chi-Square			2.021	5.843
	df			5	5
	Asymp. Sig.			.846	.322
	Monte Carlo Sig.	Sig.		.854	.334
		99% Confidence Interval	Lower Bound	.845	.322
			Upper Bound	.863	.346

a. Friedman Test

CONTROL Large P-N Interval Test Statistic[a]

Large P-N Interval				Male	Female
Best	N			9	6
	Chi-Square			7.549	.969
	df			5	5
	Asymp. Sig.			.183	.965
	Monte Carlo Sig.	Sig.		.181	.972
		99% Confidence Interval	Lower Bound	.171	.967
			Upper Bound	.191	.976
Worst	N			9	6
	Chi-Square			1.993	3.223
	df			5	5
	Asymp. Sig.			.850	.666
	Monte Carlo Sig.	Sig.		.871	.699
		99% Confidence Interval	Lower Bound	.862	.687
			Upper Bound	.880	.711

a. Friedman Test

CONTROL Large N-N Interval Test Statistic[a]

Large N-N Interval				Male	Female
Best	N			9	6
	Chi-Square			2.045	1.134
	df			5	5
	Asymp. Sig.			.843	.951
	Monte Carlo Sig.	Sig.		.854	.959
		99% Confidence Interval	Lower Bound	.845	.954
			Upper Bound	.863	.964
Worst	N			9	6
	Chi-Square			2.380	3.668
	df			5	5
	Asymp. Sig.			.794	.598
	Monte Carlo Sig.	Sig.		.806	.625
		99% Confidence Interval	Lower Bound	.796	.612
			Upper Bound	.816	.637

a. Friedman Test

CONTROL Large N1 Amplitude Test Statistic[a]

Large N1 Amplitude				Male	Female
Best	N			9	6
	Chi-Square			3.562	6.818
	df			5	5
	Asymp. Sig.			.614	.235
	Monte Carlo Sig.	Sig.		.636	.242
		99% Confidence Interval	Lower Bound	.623	.231
			Upper Bound	.648	.253
Worst	N			9	6
	Chi-Square			9.696	5.813
	df			5	5
	Asymp. Sig.			.084	.325
	Monte Carlo Sig.	Sig.		.075	.345
		99% Confidence Interval	Lower Bound	.068	.332
			Upper Bound	.082	.357

a. Friedman Test

CONTROL Large P1 Amplitude Test Statistic[a]

Large P1 Amplitude				Male	Female
Best	N			9	6
	Chi-Square			3.758	5.238
	df			5	5
	Asymp. Sig.			.585	.388
	Monte Carlo Sig.	Sig.		.612	.413
		99% Confidence Interval	Lower Bound	.599	.400
			Upper Bound	.624	.425
Worst	N			9	6
	Chi-Square			7.771	8.095
	df			5	5
	Asymp. Sig.			.169	.151
	Monte Carlo Sig.	Sig.		.172	.144
		99% Confidence Interval	Lower Bound	.162	.135
			Upper Bound	.181	.153

a. Friedman Test

CONTROL Flash N1 Latency Test Statistic[a]

Flash N1 Latency				Male	Female
Best	N			9	6
	Chi-Square			3.524	.571
	df			2	2
	Asymp. Sig.			.172	.751
	Monte Carlo Sig.	Sig.		.190	.818
		99% Confidence Interval	Lower Bound	.180	.808
			Upper Bound	.200	.828
Worst	N			9	6
	Chi-Square			4.846	.800
	df			2	2
	Asymp. Sig.			.089	.670
	Monte Carlo Sig.	Sig.		.089	.890
		99% Confidence Interval	Lower Bound	.082	.882
			Upper Bound	.096	.898

a. Friedman Test

CONTROL Flash P1 Latency Test Statistic[a]

Flash P1 Latency				Male	Female
Best	N			9	6
	Chi-Square			.074	.700
	df			2	2
	Asymp. Sig.			.964	.705
	Monte Carlo Sig.	Sig.		.993	.767
		99% Confidence Interval	Lower Bound	.991	.756
			Upper Bound	.995	.778
Worst	N			9	6
	Chi-Square			.214	7.053
	df			2	2
	Asymp. Sig.			.898	.029
	Monte Carlo Sig.	Sig.		.943	.034
		99% Confidence Interval	Lower Bound	.937	.029
			Upper Bound	.949	.038

a. Friedman Test

CONTROL Flash N2 Latency Test Statistic[a]

Flash N2 Latency				Male	Female
Best	N			9	6
	Chi-Square			2.154	2.818
	df			2	2
	Asymp. Sig.			.341	.244
	Monte Carlo Sig.	Sig.		.354	.265
		99% Confidence Interval	Lower Bound	.342	.253
			Upper Bound	.367	.276
Worst	N			9	6
	Chi-Square			2.688	1.684
	df			2	2
	Asymp. Sig.			.261	.431
	Monte Carlo Sig.	Sig.		.280	.453
		99% Confidence Interval	Lower Bound	.268	.440
			Upper Bound	.291	.466

a. Friedman Test

CONTROL Flash N-P Interval Test Statistic[a]

Flash N-P Interval				Male	Female
Best	N			9	6
	Chi-Square			.424	3.909
	df			2	2
	Asymp. Sig.			.809	.142
	Monte Carlo Sig.	Sig.		.864	.157
		99% Confidence Interval	Lower Bound	.855	.148
			Upper Bound	.872	.167
Worst	N			9	6
	Chi-Square			.828	4.095
	df			2	2
	Asymp. Sig.			.661	.129
	Monte Carlo Sig.	Sig.		.714	.146
		99% Confidence Interval	Lower Bound	.702	.136
			Upper Bound	.726	.155

a. Friedman Test

CONTROL Flash P-N Interval Test Statistic[a]

Flash P-N Interval				Male	Female
Best	N			9	6
	Chi-Square			1.226	3.000
	df			2	2
	Asymp. Sig.			.542	.223
	Monte Carlo Sig.	Sig.		.597	.246
		99% Confidence Interval	Lower Bound	.584	.235
			Upper Bound	.609	.257
Worst	N			9	6
	Chi-Square			1.742	6.348
	df			2	2
	Asymp. Sig.			.419	.042
	Monte Carlo Sig.	Sig.		.433	.042
		99% Confidence Interval	Lower Bound	.420	.037
			Upper Bound	.446	.047

a. Friedman Test

CONTROL Flash N-N Interval Test Statistic[a]

Flash N-N Interval				Male	Female
Best	N			9	6
	Chi-Square			.867	2.174
	df			2	2
	Asymp. Sig.			.648	.337
	Monte Carlo Sig.	Sig.		.697	.370
		99% Confidence Interval	Lower Bound	.685	.357
			Upper Bound	.708	.382
Worst	N			9	6
	Chi-Square			3.257	1.412
	df			2	2
	Asymp. Sig.			.196	.494
	Monte Carlo Sig.	Sig.		.231	.577
		99% Confidence Interval	Lower Bound	.220	.564
			Upper Bound	.242	.598

a. Friedman Test

CONTROL Flash N1 Amplitude Test Statistic[a]

Flash N1 Amplitude				Male	Female
Best	N			9	6
	Chi-Square			1.556	2.333
	df			2	2
	Asymp. Sig.			.459	.311
	Monte Carlo Sig.	Sig.		.579	.432
		99% Confidence Interval	Lower Bound	.566	.419
			Upper Bound	.591	.445
Worst	N			9	6
	Chi-Square			.889	.333
	df			2	2
	Asymp. Sig.			.641	.846
	Monte Carlo Sig.	Sig.		.696	.961
		99% Confidence Interval	Lower Bound	.684	.956
			Upper Bound	.708	.966

a. Friedman Test

CONTROL Flash P1 Amplitude Test Statistic[a]

Flash P1 Amplitude				Male	Female
Best	N			9	6
	Chi-Square			2.889	2.333
	df			2	2
	Asymp. Sig.			.236	.311
	Monte Carlo Sig.	Sig.		.282	.427
		99% Confidence Interval	Lower Bound	.270	.414
			Upper Bound	.293	.440
Worst	N			9	6
	Chi-Square			1.556	.333
	df			2	2
	Asymp. Sig.			.459	.846
	Monte Carlo Sig.	Sig.		.565	.952
		99% Confidence Interval	Lower Bound	.552	.946
			Upper Bound	.578	.957

a. Friedman Test

APPENDIX 1.6 Between group analysis of electrophysiology results

Large Check N1 LATENCY * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2.66	2	1.33	0.00	0.996
Within groups	290.48	10	29.05	0.76	0.666
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	380.39	2	190.2	0.54	0.592
Within groups	229.58	10	22.96	0.51	0.880

a. Analysis of Variance (Repeated Measures)

Large Check P1 LATENCY * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1432.57	2	716.28	2.93	0.073
Within groups	176.3	10	17.63	2.02	0.038
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	4268.7	2	2134.35	10.97	0.000
Within groups	87.22	10	8.72	0.59	0.818

a. Analysis of Variance (Repeated Measures)

Large Check N2 LATENCY * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1292.63	2	646.32	1.27	0.299
Within groups	160.32	10	16.03	0.53	0.868
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2841.27	2	1420.63	2.72	0.087
Within groups	193.75	10	19.38	0.57	0.832

a. Analysis of Variance (Repeated Measures)

Large Check N-P INTERVAL * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1348.7	2	674.35	2.51	0.103
Within groups	362.70	10	36.27	0.92	0.52
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2101.00	2	1051.00	3.47	0.048
Within groups	314.64	10	31.46	0.54	0.858

a. Analysis of Variance (Repeated Measures)

Large Check P-N INTERVAL * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	313.14	2	156.57	0.39	0.678
Within groups	225.31	10	22.53	0.60	0.809
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	252.04	2	126.02	0.50	0.615
Within groups	171.10	10	17.11	0.42	0.933

a. Analysis of Variance (Repeated Measures)

Large Check N-N INTERVAL * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1260.67	2	630.33	0.65	0.529
Within groups	617.16	10	61.72	1.01	0.437
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1168.51	2	584.98	0.69	0.509
Within groups	175.65	10	17.56	0.26	0.988

a. Analysis of Variance (Repeated Measures)

Large Check N1 SIZE * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	25.94	2	12.97	1.81	0.187
Within groups	4.51	10	0.45	0.77	0.653
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	48.98	2	24.49	2.64	0.093
Within groups	6.84	10	0.68	0.87	0.562

a. Analysis of Variance (Repeated Measures)

Large Check P1 SIZE * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	21.40	2	10.70	0.21	0.811
Within groups	6.43	10	0.64	0.49	0.892
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	198.74	2	99.37	2.11	0.144
Within groups	10.38	10	1.04	0.80	0.627

a. Analysis of Variance (Repeated Measures)

Small Check N1 LATENCY * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	106.37	2	53.18	0.32	0.728
Within groups	106.81	10	10.68	0.58	0.829
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1377.56	2	688.78	2.72	0.087
Within groups	63.40	10	6.34	0.22	0.994

a. Analysis of Variance (Repeated Measures)

Small Check P1 LATENCY * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1625.83	2	812.91	3.37	0.052
Within groups	105.54	10	10.55	1.19	0.302
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	3820.79	2	1910.40	9.55	0.001
Within groups	91.51	10	9.15	0.75	0.677

a. Analysis of Variance (Repeated Measures)

Small Check N2 LATENCY * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	3026.65	2	1513.32	3.89	0.035
Within groups	198.49	10	19.85	0.77	0.654
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	4112.78	2	2056.39	6.23	0.007
Within groups	348.06	10	34.81	0.84	0.588

a. Analysis of Variance (Repeated Measures)

Small Check N-P INTERVAL * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1048.24	2	524.12	2.02	0.156
Within groups	296.60	10	29.66	1.20	0.299
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	984.91	2	492.45	2.85	0.078
Within groups	74.38	10	7.44	0.18	0.998

a. Analysis of Variance (Repeated Measures)

Small Check P-N INTERVAL * GROUP Test Statistic[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	216.67	2	108.33	0.50	0.612
Within groups	177.77	10	17.78	0.55	0.852
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	33.17	2	16.58	0.07	0.937
Within groups	451.80	10	45.18	1.18	0.312

a. Analysis of Variance (Repeated Measures)

Small Check N-N INTERVAL * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2189.29	2	1094.64	2.15	0.140
Within groups	409.33	10	40.93	0.89	0.549
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1291.80	2	645.9	1.49	0.246
Within groups	440.52	10	44.05	0.51	0.882

a. Analysis of Variance (Repeated Measures)

Small Check N1 SIZE * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	43.38	2	21.74	2.17	0.136
Within groups	6.34	10	0.63	0.73	0.696
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	61.37	2	30.68	3.73	0.040[b]
Within groups	5.06	10	0.51	0.61	0.802

a. Analysis of Variance (Repeated Measures)
b. Significant difference between diffuse and focal arachnoiditis. No difference to control.

Small Check P1 SIZE * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	170.63	2	85.31	2.23	0.131
Within groups	6.69	10	0.67	0.48	0.900
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	233.86	2	116.93	2.61	0.095
Within groups	5.29	10	0.53	0.27	0.986

a. Analysis of Variance (Repeated Measures)

Flash N1 LATENCY * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	3012.09	2	1506.05	4.85	0.017
Within groups	125.08	4	31.27	1.89	0.129
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1975.66	2	987.83	2.07	0.150
Within groups	51.16	4	12.79	1.01	0.412

a. Analysis of Variance (Repeated Measures)

Flash P1 LATENCY * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1382.42	2	691.21	1.48	0.248
Within groups	116.20	4	29.05	1.28	0.293
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	1551.09	2	775.54	1.31	0.290
Within groups	181.04	4	45.26	1.42	0.243

a. Analysis of Variance (Repeated Measures)

Flash N2 LATENCY * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	320.80	2	160.40	0.21	0.816
Within groups	32.08	4	8.02	0.13	0.970
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	110.13	2	55.06	0.06	0.945
Within groups	80.73	4	20.18	0.29	0.885

a. Analysis of Variance (Repeated Measures)

Flash N-P INTERVAL * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2636.56	2	1318.28	2.12	0.143
Within groups	1214.88	4	303.72	1.25	0.302
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2.56	2	1.28	0.00	0.999
Within groups	613.72	4	153.43	0.85	0.502

a. Analysis of Variance (Repeated Measures)

Flash P-N INTERVAL * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	2219.95	2	1109.98	1.20	0.320
Within groups	684.22	4	171.05	0.55	0.700
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	4615.08	2	2307.54	2.09	0.147
Within groups	712.87	4	178.22	0.88	0.485

a. Analysis of Variance (Repeated Measures)

Flash N-N INTERVAL * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	3516.58	2	1758.29	1.10	0.350
Within groups	92.98	4	23.24	0.32	0.866
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	4414.44	2	2207.22	1.15	0.336
Within groups	162.26	4	40.56	0.61	0.660

a. Analysis of Variance (Repeated Measures)

Flash N1 SIZE * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	7.03	2	3.53	1.05	0.367
Within groups	4.16	4	1.04	0.64	0.639
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	3.65	2	1.83	0.33	0.723
Within groups	1.55	4	0.39	0.27	0.897

a. Analysis of Variance (Repeated Measures)

Flash P1 SIZE * GROUP

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	57.91	2	28.96	1.16	0.332
Within groups	7.95	4	1.99	1.02	0.408
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	41.24	2	20.62	0.97	0.394
Within groups	3.2	4	0.80	0.40	0.804

a. Analysis of Variance (Repeated Measures)

APPENDIX 1.7 Analysis of age for female only groups

AGE * FEMALE GROUP Test Statistic[c]

			AGE
Mann-Whitney U			13.5
Wilcoxon W			34.5
Z			-.722
Asymp. Sig (2-tailed)			.470
Exact Sig. [2*(1-tailed Sig.)]			.485[b]
Monte Carlo Sig.	Sig.		.516[b]
	99% Confidence Interval	Lower Bound	.504
		Upper Bound	.529
Monte Carlo Sig.	Sig.		.258[b]
	99% Confidence Interval	Lower Bound	.246
		Upper Bound	.269

a. Not corrected for ties
b. Based on 10000 sampled tables with starting seed 2000000
c. Grouping Variable: GROUP

APPENDIX 1.8 Statistical Analyses of Visual Reaction Time

VRT Within Subject Variation Test Statistic[a]

Visual Reaction Time				Male	Female
Best	N			13	13
	Chi-Square			9.400	9.308
	df			9	9
	Asymp. Sig.			.401	.409
	Monte Carlo Sig.	Sig.		.407	.415
		99% Confidence Interval	Lower Bound	.394	.402
			Upper Bound	.419	.427
Worst	N			13	13
	Chi-Square			1.899	9.859
	df			9	9
	Asymp. Sig.			.993	.362
	Monte Carlo Sig.	Sig.		.993	.367
		99% Confidence Interval	Lower Bound	.991	.354
			Upper Bound	.995	.379

a. Friedman Test

VRT for FEMALE vs MALE CONTROLS Test Statistic[d]

BEST			Mean VRT	Fastest VRT
Mann-Whitney U			15.000	18.000
Wilcoxon W			60.000	63.000
Z			-1.414	-1.062
Asymp. Sig (2-tailed)			.157	.288
Exact Sig. [2*(1-tailed Sig.)]			.181[a]	.328[a]
Monte Carlo Sig.	Sig.		.182[b]	.312[b]
	99% Confidence Interval	Lower Bound	.172	.300
		Upper Bound	.192	.324
Monte Carlo Sig.	Sig.		.091[b]	.151[b]
	99% Confidence Interval	Lower Bound	.083	.142
		Upper Bound	.098	.161
WORST			Mean VRT	Fastest VRT
Mann-Whitney U			8.000	13.000
Wilcoxon W			53.000	58.000
Z			-2.239	-1.650
Asymp. Sig (2-tailed)			.025	.099
Exact Sig. [2*(1-tailed Sig.)]			.026[a]	.113[a]
Monte Carlo Sig.	Sig.		.025[b]	.116[b]
	99% Confidence Interval	Lower Bound	.021	.108
		Upper Bound	.029	.124
Monte Carlo Sig.	Sig.		.012[b]	.057[b]
	99% Confidence Interval	Lower Bound	.009	.051
		Upper Bound	.014	.063

a. Not corrected for ties
b. Based on 10000 sampled tables with starting seed 1376818672
c. Grouping Variable: SEX
d. Mann-Whitney U test

Within Subject Variation VRT * GROUP Test Statistic[a]

BEST			Control	Focal	Diffuse
N			15	3	8
Chi-Square			7.025	15.759	10.628
df			9	9	9
Asymp. Sig			.635	.072	.302
Monte Carlo	Significance		.652	.035[b]	.303
	99% Confidence	Lower Bound	.640	.030	.291
	Interval	Upper Bound	.664	.040	.315
WORST					
N			15	3	8
Chi-Square			12.686	6.2	17.357
df			9	9	9
Asymp. Sig			.177	.720	.043
Monte Carlo	Significance		.180	.773	.036[b]
	99% Confidence	Lower Bound	.170	.762	.031
	Interval	Upper Bound	.190	.783	.041

a. Friedman test
b. Focal and diffuse groups show variation, justifying use of ANOVA with repeated measures

Visual Reaction Time * GROUP[a]

BEST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	451252.73	2	225626.37	6.29	0.007
Within groups	84294.68	18	4683.04	2.00	0.011
WORST EYE					
Source	Sum of Sq	D.F.	Mean Sq	F	Sig. Level
Between groups	515461.65	2	257730.82	6.57	0.006
Within groups	76269.93	18	4237.22	1.89	0.018

a. ANOVA with repeated measures

VRT and FVRT for CONTROL vs FOCAL Test Statistic[d]

BEST			Mean VRT	Fastest VRT
Mann-Whitney U			22.000	21.500
Wilcoxon W			28.000	27.500
Z			-0.059	-.119
Asymp. Sig (2-tailed)			.953	-.906
Exact Sig. [2*(1-tailed Sig.)]			1.000[b]	.912[b]
Monte Carlo Sig.	Sig.		1.000[b]	.933[b]
	99% Confidence Interval	Lower Bound	1.000	.927
		Upper Bound	1.000	.940
Monte Carlo Sig.	Sig.		.501[b]	.460[b]
	99% Confidence Interval	Lower Bound	.488	.447
		Upper Bound	.514	.473
WORST			Mean VRT	Fastest VRT
Mann-Whitney U			20.000	12.000
Wilcoxon W			140.000	18.000
Z			-0.296	-1.244
Asymp. Sig (2-tailed)			.767	.214
Exact Sig. [2*(1-tailed Sig.)]			.824[b]	.250[b]
Monte Carlo Sig.	Sig.		.827b	.248[b]
	99% Confidence Interval	Lower Bound	.817	.237
		Upper Bound	.837	.260
Monte Carlo Sig.	Sig.		.412b	.121[b]
	99% Confidence Interval	Lower Bound	.399	.113
		Upper Bound	.425	.130

a. Not corrected for ties
b. Based on 10000 sampled tables with starting seed 957521522
c. Grouping Variable: GROUP
d. Mann-Whitney U test to contrast to ANOVA result

VRT and FVRT for CONTROL vs DIFFUSE Test Statistic[d]

BEST			Mean VRT	Fastest VRT
Mann-Whitney U			25.000	30.500
Wilcoxon W			145.000	150.500
Z			-2.259	-1.905
Asymp. Sig (2-tailed)			.024	.057
Exact Sig. [2*(1-tailed Sig.)]			.023[a]	.056[a]
Monte Carlo Sig.	Sig.		.022[b]	.056[b]
	99% Confidence Interval	Lower Bound	.018	.050
		Upper Bound	.026	.062
Monte Carlo Sig.	Sig.		.012[b]	.026[b]
	99% Confidence Interval	Lower Bound	.009	.022
		Upper Bound	.014	.031
WORST			Mean VRT	Fastest VRT
Mann-Whitney U			22.000	33.000
Wilcoxon W			142.000	153.000
Z			-2.453	-1.743
Asymp. Sig (2-tailed)			.014	.081
Exact Sig. [2*(1-tailed Sig.)]			.013[a]	.087[a]
Monte Carlo Sig.	Sig.		.012[b]	.083[b]
	99% Confidence Interval	Lower Bound	.009	.076
		Upper Bound	.015	.090
Monte Carlo Sig.	Sig.		.006[b]	.040[b]
	99% Confidence Interval	Lower Bound	.004	.035
		Upper Bound	.008	.045

a. Not corrected for ties
b. Based on 10000 sampled tables with starting seed 1558323283
c. Grouping Variable: GROUP
d. Mann-Whitney U test

VRT and FVRT for FEMALE DIFFUSE VS FEMALE CONTROL Test Statistic[d]

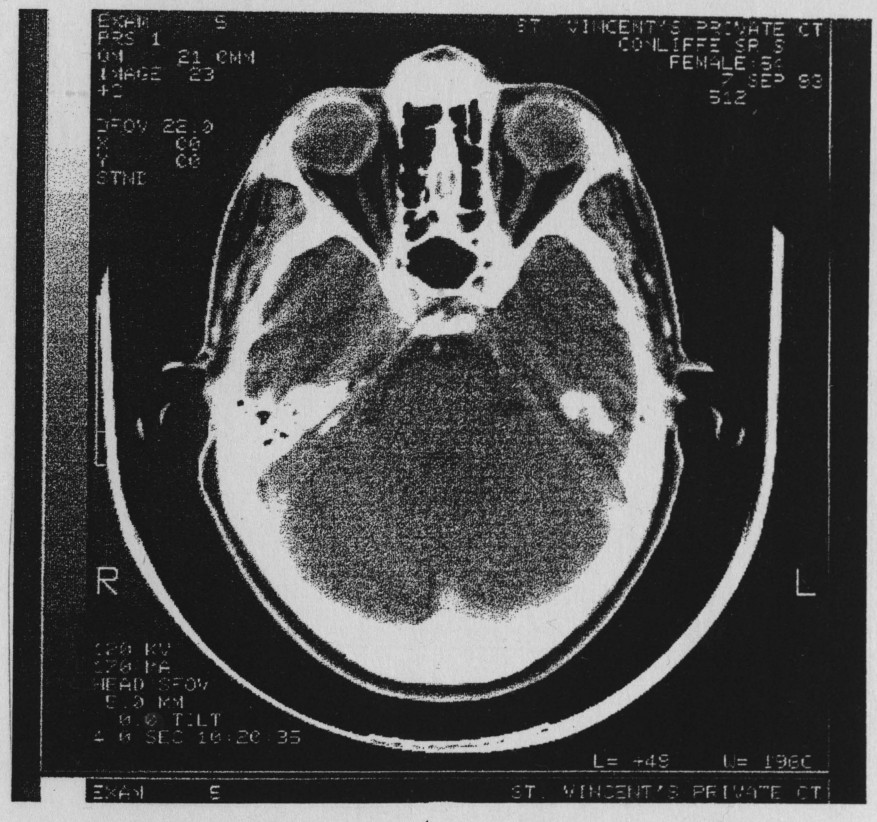
BEST			Mean VRT	Fastest VRT
Mann-Whitney U			4.000	8.500
Wilcoxon W			25.000	29.500
Z			-2.242	-1.524
Asymp. Sig (2-tailed)			.025	.128
Exact Sig. [2*(1-tailed Sig.)]			.026[a]	.132[a]
Monte Carlo Sig.	Sig.		.025[b]	.143[b]
	99% Confidence Interval	Lower Bound	.021	.134
		Upper Bound	.029	.152
Monte Carlo Sig.	Sig.		.012[b]	.071[b]
	99% Confidence Interval	Lower Bound	.009	.064
		Upper Bound	.015	.077
WORST			Mean VRT	Fastest VRT
Mann-Whitney U			3.000	5.000
Wilcoxon W			24.000	26.000
Z			-2.402	-2.082
Asymp. Sig (2-tailed)			.016	.037
Exact Sig. [2*(1-tailed Sig.)]			.015[a]	.041[a]
Monte Carlo Sig.	Sig.		.016[b]	.040[b]
	99% Confidence Interval	Lower Bound	.013	.035
		Upper Bound	.019	.045
Monte Carlo Sig.	Sig.		.008[b]	.019[b]
	99% Confidence Interval	Lower Bound	.006	.016
		Upper Bound	.010	.023

a. Not corrected for ties
b. Based on 10000 sampled tables with starting seed 1436388411
c. Grouping Variable: GROUP
d. Mann-Whitney U test

APPENDIX 2 : Arachnoiditis CT Reports

Patient 1 Axial CT Scan of 58 year old female with diffuse arachnoiditis

High signal is noted within the optic nerve of the left eye which also showed increased VECP latencies



Patient 2 Written report only

A 60 year old male, with diffuse arachnoiditis, presented a CT axial brain scan that reported "focal Myodil droplets in the right middle cranial fossa".

The VECP findings for this patient showed an increase in P1 latency for both large and small checks that was greater in the right eye (OD 123 ms and OS 118 ms).