Assessing seizure susceptibility using visual psychophysical tests

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Abstract

The spread of epileptic activity within the cortex is opposed by a powerful inhibitory restraint. We hypothesized that the same inhibitory mechanisms are likely also to underlie the phenomenon of centre-surround suppression. In this thesis, I used different non-invasive visual psychophysical assays of surround suppression to answer whether they can be used as a measurement of network state in epilepsy and as a way of predicting seizures.

We recruited 146 healthy volunteer controls and 54 patients with clinically confirmed epilepsy. Three different stimulus paradigms (motion direction discrimination, contrast detection and orientation discrimination tasks) were used to derive surround suppression indices which are believed to reflect the strength of cortical inhibition.

Our results suggest that motion and contrast surround suppression phenomena are not related. We found that suppression indices for the different tests in individual participants were not significantly correlated. In addition, multivariate regression analyses showed that motion suppression index was predicted strongly by age and seizure type, but not by seizure frequency. Specifically, we found that patients with exclusively focal epilepsy, and no history of generalization, showed significantly stronger cortical inhibition as measured by the surround suppression index compared to all other groups, including controls. In contrast, patients with focal seizures evolving into generalised seizures, and patients with generalised genetic epilepsy, showed a similar level of cortical inhibition to controls.

To answer whether psychophysical tests can be used as a way of predicting seizures, a longitudinal study was designed, deriving repeated measures of suppression indices in individuals. The results indicated no strong link between timing of seizures and suppression indices in patients.

In conclusion, visual psychophysics provides a simple and non-invasive means of assessing the state of inhibitory networks involved in the pathophysiology of epilepsy. The inability to increase activity in inhibitory networks in response to focal epileptic seizure may predict the risk of generalised seizures, which may in turn allow stratification of SUDEP risk.

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Overview of the thesis

This thesis is divided into the following chapters:

- It begins with chapter 1 with a review of epilepsy, visual psychophysics and previous clinical studies using visual psychophysics.
- Following the introduction, chapter 2 describes the materials and details of the experimental methods and analysis that were used to extract the results. It also describes participants' recruitment policies and the rationale behind recruiting Indian participants.
- Chapter 3 demonstrates the initial set of experiments and the results that were used for healthy controls to find the relationship between different visual psychophysical tests in one population. This chapter describes how the motion discrimination and the contrast detection tasks are related and what the relationship of the suppression indices is with age.
- Chapter 4 and 5 show results of visual psychophysics in patients with epilepsy and the comparison between their suppression indices with the control group. Chapter 4 explores the relationship between seizure frequency and suppression indices. Moreover, I explain whether the differences are affected by anti-epileptic drugs or the type of epilepsy. Following the results found in this chapter, Chapter 5 further investigates the possibility of a link between the measured suppression indices and seizure susceptibility in patients. Here I also compare the variation in suppression indices among patients and controls in a longitudinal study.
- Chapter 6 is a short chapter to present the results found in the India cohort and to explain whether the results support what was found in Newcastle.

- And finally, the discussion chapter will discuss the results and the practical issues regarding the use of visual psychophysics to predict seizures in epilepsy and what can be done in the future studies.

Chapter 1 Introduction

The brain consists of massively interconnected networks made up of excitatory (principal cells) and inhibitory (inhibitory interneurons) cells. In the cerebral cortex, excitatory neurons comprise around 80% of the neuronal population, while inhibitory neurons take up the remaining 20% (Hendry et al., 1987). An important feature of cortical networks is the precise interplay between these two forces, the excitation and the inhibition (Isaacson and Scanziani, 2011, Moore et al., 2010). This endlessly changing flow of excitatory and inhibitory synaptic barrages has an important role in modulating the participation of neurons in local and large scale networks (Haider and McCormick, 2009). Neural networks optimise their function using complex homeostatic mechanisms to regulate this proper interaction (Turrigiano, 2011), however, when this precise interplay breaks, epileptic seizures can occur.

Epilepsy is one of the most common neurological disorders and around 1% of the world's population (about 50 million people) suffer from epileptic seizures (WHO, 2006). Epilepsy is characterised by epileptic seizures. The International League Against Epilepsy (ILAE) defines an epileptic seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005). According to their most recent report (Fisher et al., 2014) epilepsy is "*a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition*". They defined three characteristics for epilepsy: "*(1) At least two unprovoked seizures occurring 24 hours apart; (2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%)*

after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome".

Epilepsy is defined as the occurrence of "paroxysmal events" which refer to intermittent and inherent unpredictability of these events. The underlying pathophysiology is of periods of neuronal hypersynchrony which can be observed as large amplitude discharges on the EEG (Electroencephalogram). The clinical manifestation ranges from almost nothing (subclinical seizures) to status epilepticus which is a life-threatening medical and neurologic emergency (Al-Mufti and Claassen, 2014).

Epilepsy is mainly treated by anti-epileptic drugs (AEDs) and in some cases by surgically removing the seizure focus. However considering side effects and the unexpected nature of seizures, epilepsy can significantly interrupt a patient's life (plus social disadvantages, such as unemployment and stigma). Most patients respond to AEDs but some do not and continue to have seizures (Loscher et al., 2013). The unpredictability of seizures has a major effect on patients' lives since it makes it almost impossible to mitigate against. Therefore, there has been a lot of effort in this area, from basic understanding of epilepsy to different ways of predicting seizures, to improving the living conditions of patients with epilepsy. Anything that allows patients in this group to predict their seizures would be hugely beneficial. The requirements of such a predictive tool are that it should be easy to use in the patient's own home which means it does not need an EEG or other specialized equipment, it reliably predicts seizures without producing too many false alarms, and does it sufficiently far before the seizure to allow the patient to be able to manage it.

Epilepsy is believed to stem from a lack of proper balance between inhibition and excitation. The mechanism of action of AEDs are still not exactly known. However, they are aimed to improve the relationship between inhibitory and

excitatory forces through reducing the excessive electrical activity in the brain and making inhibitory forces more effective. Of course, inhibition has many other functions within the brain beyond avoiding epilepsy. For example, it is believed to underlie many aspects of vision (Allman et al., 1985b, Jones et al., 2002, Solomon et al., 2004). Recently, there has been considerable interest in exploiting this fact to use non-invasive visual psychophysical tests as an assay of cortical inhibition. The term psychophysics was first introduced by German physicist and psychologist Gustav Theodor Fechner in 1860 (Kingdom and Prins, 2010). Gescheider (1997) in his classic book of "Psychophysics: the fundamentals" defines psychophysics as *"the scientific study of the relation between stimulus and sensation"*. Psychophysics can be applied to any sensory system from vision and hearing to taste, smell and touch (Kingdom and Prins, 2010). In fact, psychophysics is a non-invasive way of analysing a subject's response to systematically designed changes to the physical properties of a stimulus. This is done by extracting a "threshold" or "just noticeable difference" from a psychometric function (Equation 2.8) by relating a quantitative quality of a stimulus to the probability of a particular judgement (Read, 2015) when the probability of a correct judgement exceeds a pre-defined level.

Intriguing results have been found in several clinical groups with impairment in cortical levels of the inhibitory neurotransmitter GABA (Gamma-Aminobutyric acid). However, this has not so far been examined in the context of epilepsy and here we investigated visual psychophysics as a potential clinical tool for assessing seizure risk.

This chapter will start with basic introduction of epilepsy and different types of seizures. I then explain surround suppression and visual psychophysics with example of previous clinical studies and their findings. I will also explain the

relevance of using visual psychophysics for epilepsy. And lastly, I explain the aims of my thesis which will be further elaborated in the following chapters.

1.1 Epilepsy and timing of seizures

1.1.1 Classification

It is important to make a clear distinction between classification of epilepsy and classification of seizures. Seizures are a separate category to epilepsies, and epilepsies are a separate category to aetiologies. It is very difficult to classify epileptic seizures. Because of the wide verity of seizure types, their underlying aetiology and the effect on patients (for example with or without impaired consciousness) finding a single classification system has proven challenging, and several systems have been proposed over the years. There are multiple different types of epilepsy which are far greater than variation in other neurological disorders such as migraine, schizophrenia and depression.

In general, epilepsy can be categorised by the seizure localisation into two groups of generalised and focal. Generalised seizures include seizures that engage bilaterally distributed networks but do not necessarily mean involvement of the entire cortex (Berg et al., 2010). Examples of epilepsies with generalised seizures are genetic generalised epilepsies (GGE), childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalised tonic-conic seizures (EGTCS) (Scheffer et al., 2016). Focal epileptic seizures are defined as seizures that start within networks in one hemisphere of the brain (Berg et al., 2010). Examples are different types of temporal lobe and frontal lobe epilepsy. According to the new terminology by the ILAE, description of focal seizures should include the degree of impairment of consciousness. For example, the term complex partial seizures that means impairment of consciousness in focal epilepsy is now replaced with the term

“dyscognitive”. Classification of seizures based on these two groups according to ILAE can be seen in Figure 1.1 (Berg et al., 2010).

Seizures can have multiple different causes and can be classified as acute symptomatic and unprovoked. A symptomatic seizure is caused by a previously known or suspected disorder of central nervous system which is believed to have increased the risk of developing seizure, for example a seizure that is developed after a stroke, brain trauma, drug or alcohol withdrawal, an CNS infection or a toxic insult. On the other hand, an unprovoked seizure is a seizure of an unknown aetiology which is not associated with a previous CNS insult known to increase the risk of developing seizure.

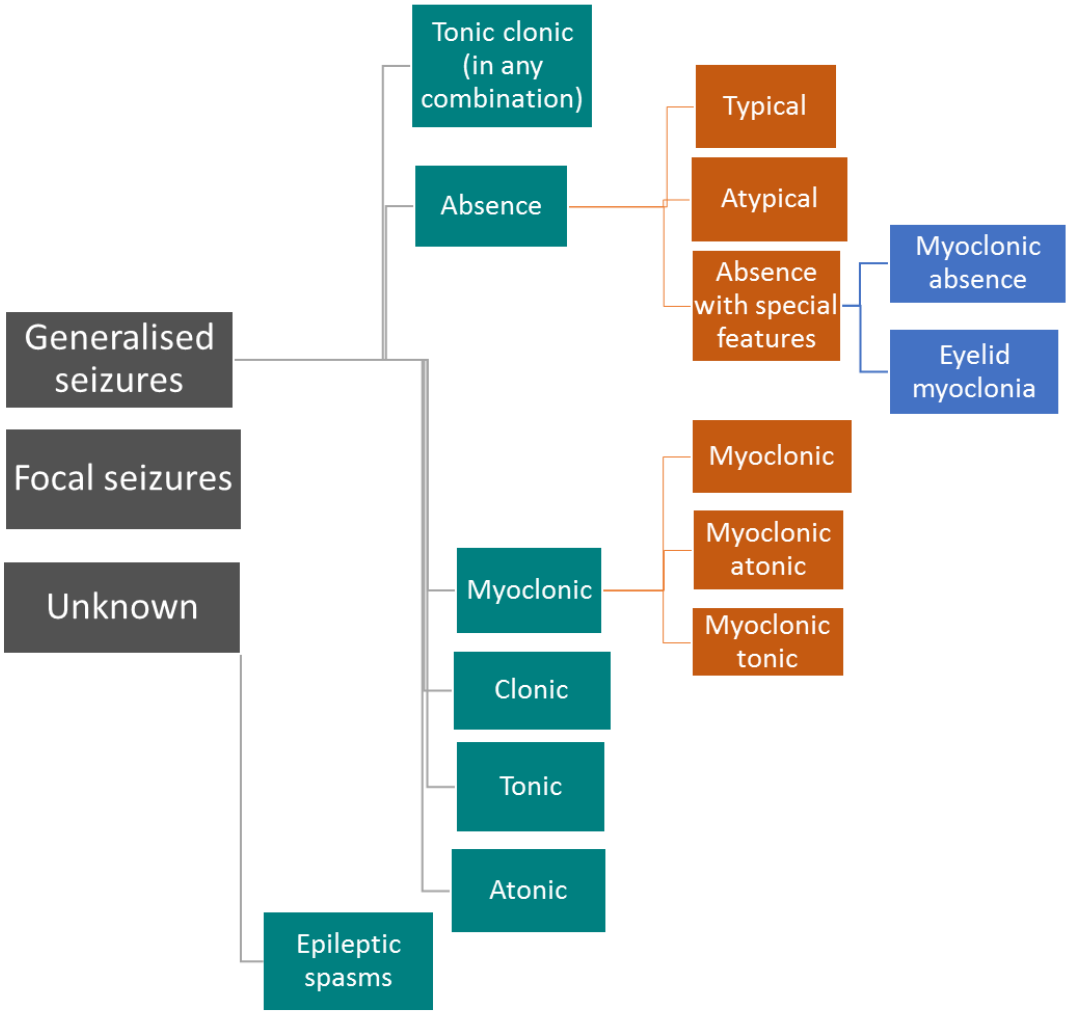


Figure 1.1. Classification of seizures into generalized and focal seizures, reproduced from Berg et al. (2010).

Many patients cannot be categorised into one group, mainly because of overlapping features with both generalised and focal seizures. Therefore, aetiology or the underlying cause of epilepsy needs to be taken into account. Berg et al. (2010) have recommended three categories: genetic, structural-metabolic (with structural lesions and stroke, trauma, infection) and unknown causes. Details of aetiology of recruited patients can be found in Appendix 1 and Appendix 2. There are also updated documents of ILAE based on the proposals and feedbacks after the final Berg et al. (2010) paper on seizure classification,

and on epilepsy classification which are not yet finalised (http://www.ilae.org/visitors/centre/Class-Seizure.cfm).

Our hypothesis was that if visual psychophysics is a non-invasive way of measuring cortical inhibition, then it may be possible to use it to assess patients in which inhibition is believed to be compromised. Specifically, we speculated that visual psychophysics could be used to assess patients with epilepsy, as a potential assay to show any deficit in surround suppression in the form of altered thresholds in comparison with controls.

1.1.2 Surround suppression and the role of excitation and inhibition in epilepsy

GABA is the main inhibitory neurotransmitter in the adult mammalian central nervous system (CNS). In the CNS, inhibition primarily occurs through GABAergic signalling onto ionotropic $GABA_A$ receptors, which results in an inward chloride (Cl^-) conductance that hyperpolarizes the cell (Lee and Maguire, 2014, Farrant and Nusser, 2005). A lot of experimental and clinical evidence have demonstrated the role of GABA in epilepsy. GABA agonists such as Muscimol and Progabide have anticonvulsant effect, and GABA antagonists such as bicuculline and picrotoxin are pro-convulsants (Treiman, 2001). Drugs that inhibit GABA synthesis, such as 4-deoxypyridoxine are linked to epilepsy (Treiman, 2001) and drugs such as barbiturates that increase GABA-mediated inhibition have anticonvulsive effect.

Experimental evidence of different brain regions (Nusser and Mody, 2002) show that $GABA_A$ receptors located at synapses generate a spatially and temporally distinctive type of inhibition than those found extrasynaptically (Kaneda et al., 1995). Phasic (synaptic) inhibition is short intermittent bursts of inhibition mediated by receptors at the post synaptic neuron with low affinity for GABA

binding critical for information processing. Whereas, tonic (extra-synaptic) inhibition is a constant, long-lasting inhibition activated by GABA in the extracellular space (Mody, 2001, Farrant and Nusser, 2005) with an important role in neuronal excitability in the brain (Brickley et al., 1996). In thalamocortical neurons of genetic models of epilepsy, phasic $GABA_A$ inhibition is either unchanged or increased, whereas tonic $GABA_A$ inhibition is increased both in genetic and pharmacological models (Crunelli et al., 2011). This enhanced tonic inhibition is required for absence seizure generation (Cope et al., 2009). Some studies have shown implication of malfunction in the astrocytic GABA transporter GAT-1 in genetic models (Crunelli et al., 2011).

Inhibitory configuration of the brain as a network depends on how its excitatory and inhibitory elements are interconnected. These patterns of wiring are categorised as feedback, feed-forward and lateral inhibition. A feedback inhibitory circuit provides a regulatory mechanism in which increase in firing of a principle cell, increases the interneuron's firing which in turn may decrease the principle cell's overall output. In a feed-forward inhibitory circuit, increase in the firing of an interneuron results in reduction of the discharge in a principle cell. The term "lateral inhibition" or "surround suppression" refers to the fact that an excited neuron can reduce the activity of its surround or neighbouring area. An influential early study of unit recording of cortical neurons done by Mountcastle and Powell (1959) showed such inhibitory activity in the surrounding cortical area following focal stimulation. Similar surround inhibition was also seen around focal pathological lesions induced by penicillin injections in cat hippocampus (Dichter and Spencer (1969a), Dichter and Spencer (1969b),Prince and Wilder (1967)) and also observed in ferret cerebral cortex using optical imaging (Schwartz and Bonhoeffer (2001)). These studies showed inhibitory postsynaptic currents in the surrounding area of the excited focus, giving rise to

the idea of a protective “surround inhibition” (Prince and Wilder, 1967). More recently, a few studies used electrophysiology and in vitro imaging in artificially prepared brain slices of rodents (in vitro models of epileptiform discharges), to show that areas of hypersynchronous activity were engaging all neurons. However, when the activity was going to the surrounding territories, they were not immediately recruited and were opposed, for a period of time, by a strong feed-forward inhibitory response (Cammarota et al., 2013b, Trevelyan et al., 2007, Trevelyan et al., 2006). It is believed that, in healthy brains, this inhibitory effect efficiently stops local areas of hypersynchronous activity developing into an epileptic seizure.

There are a number of pathological reasons for seizure generation, such as neural reorganization and changes in the release of neurotransmitters. Neural reorganization can cause hyper-excitability which increases the likelihood of the generation of recurrent seizures (Olney et al., 1972, McNamara, 1994). Reduction in the levels of GABA results in less inhibition and elevated levels of glutamate neurotransmitter have been reported in human brain tissues and animal models of epilepsy (Cho, 2013). Glutamate induced excitotoxicity has been linked to neuronal death in epilepsy (Haglid et al., 1994, Cho, 2013) and a lot of studies have suggested a link between excessive extracellular glutamate in the hippocampus to the pathophysiology of seizures in patients with medically intractable mesial temporal love epilepsy (Eid et al., 2004, Cavus et al., 2005, Olney et al., 1986, Olney et al., 1972). Astrocytes, the largest subgroup of glia cells, have a crucial role in mostly regulating the extracellular levels of glutamate neurotransmitter (Coulter and Eid, 2012). A malfunction in the glutamate degrading enzyme, glutamine synthetase, has been reported in astrocytes of the epileptogenic hippocampus in a subset of patients with temporal lobe epilepsy (TLE) (Eid et al., 2004). This deficiency in astrocytes has been linked to

extracellular accumulation of glutamate and seizure generation in mesial temporal lobe epilepsy (Eid et al., 2008).There are several ways that the inhibitory effect might fail to stop the spread of a seizure (Trevelyan and Schevon, 2012). One possibility is mutations in interneuron-specific sodium channel Nav1.1 or in glial cells which causes fast spiking interneurons to be less excitable (Trevelyan and Schevon, 2012). Also, changes in gene expression might cause pyramidal neurons become more excitable and some less, and therefore break the interplay between inhibition and excitation (Sloviter, 1987). Another possibility is short term depression where interneurons stop firing due to depolarizing block which in turn causes a change in the GABAergic effect (Trevelyan and Schevon, 2012, Trevelyan et al., 2006, Ziburkus et al., 2006). Another crucial change is an increase in postsynaptic chloride levels due to intense neuronal firing that will shift the membrane potential to a more depolarized level (Staley et al., 1995, Trevelyan and Schevon, 2012).

Reduction in inhibition is not the only instance of triggering a seizure. There is evidence of increasing inhibition that promotes seizure generation (Snodgrass, 1992). For example, Tiagabine which increases the level of GABA by blocking GABA transporter 1 (GAT-1) (Brodie, 1995) has been shown to trigger non convulsive status epilepticus in some patients with lesional focal epilepsy (Vinton et al., 2005). Moreover, abnormalities of GABAergic function have been observed in genetic and acquired animal models of epilepsy suggesting that possible synchronization effects of GABA interneurons may result in paradoxical facilitation of some types of epileptic discharges in these animal models (Treiman, 2001).

Of course all of these electrophysiological studies were done in animals, and so it is important to investigate whether the same spatial pattern of inhibition takes place in spontaneous (in opposed to pharmacologically induced seizures in

animal models of epilepsy) seizures in humans. A study done by Schevon et al. (2012) took advantage of recent development of multi-electrode arrays for use in humans to record temporal and spatial resolution of recorded seizures and showed that human seizure recordings have remarkable similarities with animal studies of an inhibitory restraint. In fact, these recording have demonstrated two separate spatial territories: the ictal core (the recruited area with increase in synaptic activity) and penumbral territories (restrained areas surrounding the focus of ictal activity with a fractional increase in unit activity) (Merricks et al., 2015).

As mentioned before, the underlying pathologies in epilepsy are very complex, but almost all involve GABAergic inhibitory mechanisms in some way.

1.1.3 Drugs affecting inhibition

Anti-epileptic drugs (AEDs) are a means of controlling symptoms of epilepsy and the modern use of them started from 1912 with the discovery of phenobarbital which was at first mainly used to induce sleep (Sills, 2011). Since then a lot of new drugs have emerged in the market, however the percentage of people who do not respond to AEDs has not been changed (between 20-30%) (Loscher et al., 2013).

There are three main mechanisms of AEDs that are known: actions on voltage-gated ion channels (blockade of voltage-gated sodium and calcium channels, activation of voltage-gated potassium channels), enhancement of GABA-mediated inhibitory mechanisms or decreases of glutamate-mediated excitatory mechanisms (Sills, 2011).

As we are using visual psychophysics as a non-invasive way of measuring inhibition, it is necessary to consider the effect of AEDs on the measured surround suppression. In particular, some classes of AEDs including benzodiazepines, and barbiturates act on $GABA_A$ receptors resulting in rise in

response to released GABA. Each class however binds to a different site on the receptor and influences the chloride channel opening in a different way. Barbiturate AEDs increase the duration of chloride channel opening and benzodiazepines change the frequency of chloride channel opening (Sills, 2011).

In addition, patients with prolonged use of AEDs are believed to have impaired visual performance such as mild diplopia, blurred vision and nystagmus (Roff Hilton et al., 2004, Verrotti et al., 2007). A study done by Nousiainen et al. (2000) compared contrast sensitivity in patients with epilepsy who were treated with Vigabatrin or Carbamazepine with healthy controls and reported a reduced contrast sensitivity in the patients group.

In another study the influence of single oral dosages of Carbamazepine, Valproic Acid, Vigabatrin, Lamotrigine and Gabapentin on visual perception was investigated in healthy volunteers to only account for the effect of AEDs without the possible influences of epilepsy (Steinhoff et al., 1997a). They reported an increase in the critical flicker fusion frequency only after Vigabatrin and Gabapentin. However, the visual stimuli used here are all fairly low in temporal frequency and any change in the flicker fusion is highly unlikely to affect perception.

1.2 Inhibition in the visual system

Inhibitory mechanisms are a universal property of visual information processing. Inhibition in visual system was first described in details by Hartline and colleagues in 1956 where they used logarithmic equations to describe the interaction between excitatory and inhibitory mechanisms and surround suppression in the retina of the horseshoe crab (Limulus) (Hartline et al., 1956).

Motion representation starts in the primary visual cortex (V1). The projections then go through middle temporal (MT, V5) and medial superior temporal area

(MST) and end at higher areas of the parietal and temporal lobes (Liu and Newsome, 2003).

1.2.1 MT

V5 or middle temporal area (MT) is a region of extrastriate visual cortex that receives direct projections from the primary visual cortex (V1) and V2. Extensive evidence of physiological studies demonstrated that most MT cells are highly sensitive to the direction of the moving stimulus meaning that each single neuron in MT selectively responds to a preferred direction of visual stimuli on the retina (Maunsell and Van Essen, 1983, Albright, 1984). This suggests that MT is involved in perceiving motion. In addition, Albright et al. (1984) demonstrated that MT neurons are grouped in cortical columns with similar preferred direction. DeAngelis and Newsome (1999) also showed that MT neurons play an important role in stereoscopic depth perception and are clustered according to their preferred disparity selectivity. In addition, studies have shown that many neurons in V1 of macaque monkey are also direction selective and therefore speculated that V1 is also involved in motion analysis (Maunsell and Van Essen, 1983, Dow, 1974, Wang and Yao, 2011). The difference between MT and V1 in motion processing is that V1 has smaller number of direction selective neurons and smaller receptive fields than MT neurons (Maunsell and Van Essen, 1983). Another property of most neurons in MT is that they are sensitive to the speed of the visual stimuli (Maunsell and Van Essen, 1983, Albright, 1984, Okamoto et al., 1999, Perrone and Thiele, 2001, Perrone and Thiele, 2002) making each of them respond to a certain speed of stimulus movement independent of the spatial and temporal frequency of the stimulus. Evidence of primate research has shown that lesions in MT and MST can diminish performance on speed discrimination tasks (Liu and Newsome, 2003, Newsome et al., 1985, Dursteler and Wurtz, 1988).

1.2.2 Centre surround organization

MT neurons have well defined classical receptive fields that are arranged in a topographic representation of the visual field (Baker et al., 1981, Allman and Kaas, 1971, Maunsell and Van Essen, 1983) to integrate spatial and temporal information. Allman et al. (1985a) for the first time demonstrated that receptive fields of neurons in the MT visual area extends beyond the classical receptive field with the surrounding area much larger than the area of the classical receptive field. The surrounding region is direction and speed sensitive and antagonistic to the response from the classical receptive field (CRF) (Allman et al., 1985a). In primates the antagonistic centre-surround receptive field organization is a ubiquitous property that can be found in V1 (Jones et al., 2001), medial superior temporal (MST) (Eifuku and Wurtz, 1998), superior colliculus (Davidson and Bender, 1991) and MT (Allman et al., 1985a, Tanaka et al., 1986, Born and Tootell, 1992, Bradley and Andersen, 1998). A typical MT neuron will respond well if the centre of its receptive field is stimulated in the preferred direction. However, in a centre-surround MT neuron if the moving stimulus extends beyond its centre receptive field and into the surround, then the response will be reduced (Tadin and Lappin, 2005, Allman et al., 1985a). Evidently, the response to a large background motion is a reduction in the number of spikes (Figure 1.2). Centre-surround organization increases the neural responses to spatially different parts of stimuli (for example edges) and suppresses responses to unvarying regions of the stimuli (Tadin, 2015). One theory is that spatially different regions of the stimuli have vital information for the visual motion processing, while uniform areas carry less revealing information (Nakayama and Loomis, 1974).

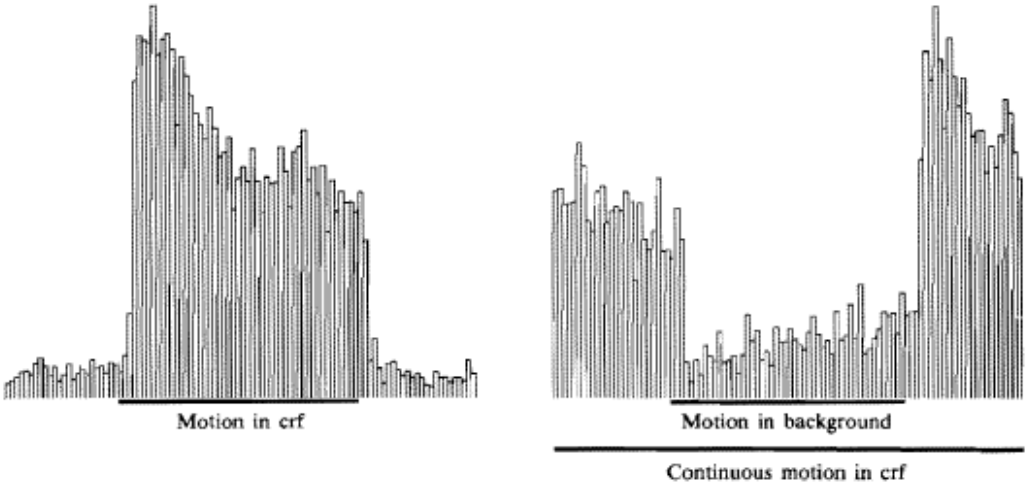


Figure 1.2. Figure is depicted from *Allman et al. (1985a)*. Left: histogram shows responses of 42 neurons in MT of an owl monkey to random dots moving for a 2 second period in preferred direction in their classical receptive field (CRF) with a static background. Right: histogram shows responses of the same neurons with continuous stimulation in the preferred direction within their CRFs and then with a 2 second test of the moving random dots in their preferred direction in the surround.

A distinctive feature of the interaction between the centre and surround of the receptive field of cortical cells is its orientation specificity (Angelucci and Bullier, 2003), meaning that the extent of facilitation or suppression of the centre response following a simultaneous stimulation of the surround and centre, depends on the relative orientation and direction of motion of stimuli in these two regions (Angelucci and Bullier, 2003, Jones et al., 2002, Sillito et al., 1995). When the stimuli in the centre and surround have similar orientation, the centre-surround interactions are reported to be suppressive, however this interaction can be less suppressive or in fact facilitatory when the centre and surround have orthogonal orientations of motion (Albright, 1984, Blakemore and Tobin, 1972, DeAngelis et al., 1992, Angelucci and Bullier, 2003). The centre-surround interactions in retina or LGN neurons are non-orientation selective (Felisberti and Derrington, 2001). However, the orientation selectivity of cortical cells

points to the fact that intracortical processing plays an important role in the generation of cortical modulatory surrounds (Angelucci and Bullier, 2003). Horizontal or lateral connections and feedback connection from extrastriate cortex have an important role in eliciting inhibitory activity that mediates surround responses in V1 (Angelucci and Bullier, 2003). A similar delay to propagation of excitatory activation which is believed to be mediated by horizontal connections, has been reported in the orientation surround suppression relative to the response of the centre. Therefore, it is likely that some of the centre-surround interactions in V1 neurons are mediated by horizontal connections. However, for longer distances in the visual field, feedback connections are the most likely substrate for the surround suppression. A lot of studies have reported lack of surround suppression after inactivation of MT, suggesting that feedback connections from MT have strong effect on the centre-surround suppression of neurons in lower order areas in the visual system (Hupe et al., 1998, Bullier et al., 2001). In fact, feedback connections combined with horizontal connections act as a non-linear model to boost the gain of the centre mechanism and to generate the centre-surround interactions (Angelucci and Bullier, 2003, Bullier et al., 2001, Kim and Freeman, 2014).

An interesting property of MT centre-surround neurons is that contrast plays an important role in their behaviour to motion (Figure 1.3). Pack et al. (2005) showed that some MT neurons respond stronger to a large low contrast stimulus than to one in high contrast and argued that this behaviour is in line with the fact that visual system reduces redundancy at high contrast while preserving sensitivity at low contrast by changing suppression to facilitation (Tadin et al., 2003, Tadin, 2015). Tadin et al 2003 argues that at high contrast, the computational benefits of surround suppression are more important than the necessary decrease in neuronal activity and reduced sensitivity. At low contrast

however, high sensitivity is crucial, therefore makes functional sense that receptive field organization shifts from surround suppression to spatial summation (Tadin, 2015, Tadin et al., 2003).

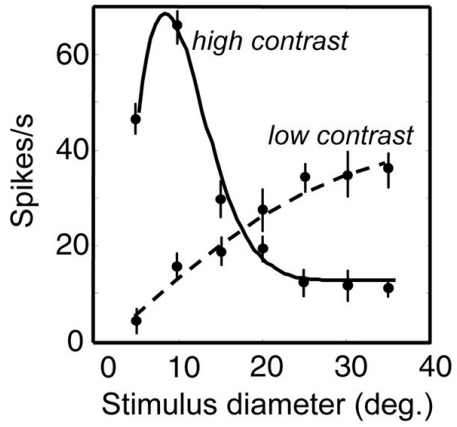


Figure 1.3. Depicted from (Pack et al., 2005). Figure shows the dependency of the neural response to stimulus contrast. Here size tuning of one MT neuron at low (dashed line) and high (solid line) contrast is shown. Error bar represent standard error of the mean.

Along with neurophysiological studies that showed the existence of surround suppression in the analysis of motion, there were a lot of psychophysical studies that reported results consistent with neurophysiological surround suppression. Motion discrimination of brief, large moving gratings improves for human observers with increasing contrast at low contrasts, however with further increases in contrast performance declines (Derrington and Goddard, 1989). Verghese and Stone (1996) showed that dividing a large moving stimulus into smaller parts improved speed discrimination and suggested suppressive mechanisms to be responsible. More recently, Tadin et al. (2003) showed that at low contrast motion discrimination, measured by duration thresholds, can be improved by increasing the size of the moving stimulus. Authors suggested this is the perceptual consequence of spatial summation where surround suppression shifts to facilitation at low contrast (Pack et al., 2005). Conversely,

at high contrast increasing the size of the stimuli worsens the motion discrimination duration thresholds. Authors have attributed these phenomena to the perceptual consequence of neurophysiological surround suppression and referred to it as “spatial suppression”. Tadin et al. (2003) demonstrated that spatial summation is a basic characteristic of motion processing, but only in low contrast conditions. In addition, they showed the transition between spatial summation and spatial suppression happens from contrast of 5.5% upwards (Tadin, 2015) and the biggest increase in duration threshold was for Gabor patches larger than 2.7° in width which made the authors to speculate the existence of a “critical size” (Tadin et al., 2003). This critical size is similar to foveal MT receptive fields of neurons in macaque monkey (Raiguel et al., 1995) and the contrast dependency of spatial suppression matches with a population of neurons in MT (Pack et al., 2005). In addition, as receptive field of motion sensitive MT neurons enlarges with increase of retinal eccentricity (Raiguel et al., 1995, Albright, 1984), Tadin et al. (2003) tested the hypothesis of whether the increase of eccentricity at high contrast would change the effect of size. They showed that with increase of eccentricity, duration thresholds decreased for all sizes and there was almost no effect at the largest eccentricity (54°) meaning that the critical size increases with increasing eccentricity. For all these reasons, they speculated that psychophysical spatial suppression has characteristics similar to centre-surround receptive fields of MT neurons and are, at least in part, a behavioural match to surround suppression in MT (Tadin et al., 2003).

1.3 Previous clinical studies

Abnormalities in cortical inhibition and excitation has been shown in a range of conditions, such as senescence (Leventhal et al., 2003), autism (Rubenstein and Merzenich, 2003), schizophrenia (Wassef et al., 2003, Yoon et al., 2010), migraine (Aurora and Wilkinson, 2007), depression (Sanacora et al., 1999) and in epilepsy (Stief et al., 2007, Sloviter, 1987, Jefferys and Whittington, 1996, Bernard et al., 1999, Andre et al., 2001).

If abnormality in excitation-inhibition could selectively affect different areas of visual cortex, the various metrics of psychophysical surround suppression could be differentially impacted (Yazdani et al., 2015). On the other hand, if cortical surround suppression reflects whole-organism properties such as genetics, age (Betts et al., 2009, Betts et al., 2012, Betts et al., 2005) or IQ (Melnick et al., 2013, Tadin, 2015), or if surround suppression in higher visual areas is "inherited" from processing in V1 (Tsui et al., 2010), then the various metrics would reflect a single fundamental neuronal property. Furthermore, if the level of surround suppression changes over time and determines whether a seizure occurs, then changes in visual psychophysics might be a useful predictor of seizures.

Tadin et al. (2003) demonstrated that a perceptual consequence of surround suppression in motion analysis can be observed as impaired perception of large, high contrast moving stimuli. Therefore, any abnormality in this impairment can be predicted to be a result of impairment in surround suppression. Consequently, any improvement in perception of large, high contrast moving stimuli (better than normal perception), can perhaps predict an underlying deficit in the surround suppression.

In essence, visual psychophysics has the potential to cast light on the underlying pathology in conditions with known compromised excitation-inhibition and could also provide clinically useful information about individual patients.

In the following section I will discuss a number of studies that have used visual psychophysics to find more information about a particular condition.

1.3.1.1 Recent work in aging

The first study that tested spatial suppression in a particular group was Betts et al. (2005) who studied changes in an aging population. They divided their participants into two groups of "younger" with mean age of 23 years old and "older" with mean age of 68, and reported that duration thresholds were higher for the older participants in the small stimuli (size= $2\sigma = 0.7°$) at all contrasts but not different between the two groups for the large stimuli (size= $2\sigma = 2.7°$). Moreover, they reported that younger participants showed spatial summation for all stimulus sizes at low contrast, and switched to spatial suppression as the stimulus size increased. They speculated that the better than normal duration thresholds for their older participants in large high contrast or the fact that they need less time to discriminate the direction of moving stimulus, is age related and caused by a reduction in efficacy of cortical inhibition with age (Leventhal et al., 2003, Eysel et al., 1998) and weakening of surround suppressive centre surround mechanisms (Betts et al., 2005).

In a contrast detection task, Serrano-Pedraza et al. (2014) however, found no effect of age. They examined the ratio of contrast thresholds for a grating patch with a parallel surround to the threshold for an isolated patch (no-surround condition). Similarly, in studies that I present in this thesis, and that are now published, we also found a lack of effect of age in a contrast detection task and showed that the relationship between suppression index and age was only significant in a motion discrimination task (Yazdani et al., 2015).

In addition, Karas and McKendrick group have reported an increase in surround suppression for older adults in some cases in a contrast discrimination task, a

result inconsistent with a broad age-related decrease in suppression strength (Karas and McKendrick, 2009, Karas and McKendrick, 2011, Karas and McKendrick, 2012, Karas and McKendrick, 2015). They showed that supra-threshold patches appear lower contrast when presented with a parallel surround than when presented in isolation, and this surround suppression is higher for older adults (65–70 years old) than for younger ones (18-30 years old). They argued that this is a result of a reduction in the magnitude of brightness enhancement in their elderly group and related to neuronal synchronization (Karas and McKendrick, 2009).

Another study sought to study the effect of senescence on orientation discrimination (Delahunt et al., 2008) as single unit recordings have shown reduction of orientation tuning of individual neurons with increasing age in macaque cortical areas V1 and V2 (Schmolesky et al., 2000, Yu et al., 2006). They found no difference between the younger (range: 20-30 years old) and older (range: 65-85 years old) groups.

Similar to aging, recent results suggest that children may have less GABAergic inhibition (Boley et al., 2005, Pinto et al., 2010). In a motion discrimination task, Lewis et al. (2008) showed that 5-year old children in a motion discrimination task performed worse than adults for small but not big stimuli and had weaker inhibitory surrounds.

In conclusion, what is clear is that this is a very complex field where many different stimuli and tasks have been used which are presumed to measure surround suppression. However, results presented in chapter 3 indicate that these tasks might be affected by different mechanisms and a simple term of surround suppression covers a great number of distinct neuronal mechanisms.

1.3.1.2 Recent work in schizophrenia

A lot of studies have shown neural deficit in patients with schizophrenia. There is evidence of hypofunction in one of glutamate receptors (NMDA) in patients with schizophrenia (Olney and Farber, 1995, Moghaddam, 2003). Moreover, the concentration of GABA is about 10% lower in patients with schizophrenia (Yoon et al., 2010, Wassef et al., 2003). There is also a great body of knowledge about the impairment of cognitive processing and in particular visual perception in schizophrenia. Examples are reduced contrast sensitivity (Slaghuis, 1998, Keri et al., 2002), altered visual context processing (Uhlhaas et al., 2004), broader orientation tuning (Rokem et al., 2011).

A lot of studies have used visual psychophysics to study this group of patients. Tadin et al. (2006) examined the integrity of centre surround mechanisms in motion perception of patients with schizophrenia and showed patients have weaker surround suppression than controls and those with the most severe symptoms have the weakest suppression. Another study used a contrast discrimination task in which observers had to indicate whether there was a difference in contrast between one target and the other seven segments of an annulus (Yoon et al., 2009). They demonstrated that patients with schizophrenia had significantly lower surround suppression index compared to controls in parallel surround, but no difference among the groups in the orthogonal surround suppression. Hence, they concluded that patients with schizophrenia have abnormal surround suppression which is related to orientation.

In a different study using contrast detection thresholds in a four alternative forced-choice task (4AFC) Serrano-Pedraza et al. (2014) supported the previous finding and showed that patients with schizophrenia had significantly lower thresholds than controls in the parallel surround condition.

Different results have been reported in a study of judgement of direction in a random moving dot paradigm with and without a surround in controls and patients with mild symptoms, which showed increased centre surround suppression in patients (Chen et al., 2008).

Work done by Yang et al. (2013a), Yang et al. (2013b) using different visual tasks (luminance, size, contrast, orientation and motion) showed that weak surround suppression in patients with schizophrenia in one of these perceptual domains did not mean similar abnormalities existed in another visual task. This means that the abnormal visual context processing in schizophrenia is selective and is not a global dysfunction. Tibber et al. (2015) also came to a similar conclusion, showing that distinct visual dimensions are differentially affected in schizophrenia and in particular judgements of visual orientation are significantly impaired in patients with schizophrenia.

1.3.1.3 Recent work in major depression

Animal models of depression suggest a dysfunction of GABAergic inhibition and GABA agonists have anti-depressant effect in these models (Petty, 1995, Golomb et al., 2009, Petty et al., 1992, Kalueff and Nutt, 2007). The deficit in levels of inhibition among patients and healthy controls has also been shown by magnetic resonance spectroscopy (MRS) (Sanacora et al., 1999, Sanacora et al., 2003).

Golomb et al. (2009) hypothesised that given patients with depression have decreased spatial suppression, they might exhibit better performance in a similar motion discrimination task to Tadin et al. (2003). In fact, these patients showed enhancement in motion perception compared to age matched controls. Additionally, those patients who had depression for a longer period of time performed the best in the high contrast motion discrimination task.

1.3.1.4 Recent work in autism

Patients with autism may also suffer from deficits in visual motion processing. Bertone et al. (2003) showed the deficit is only observed in second-order (texture-defined) stimuli in patients with autism compared to healthy participants.

In a motion direction discrimination task in children with autism, Foss-Feig et al. (2013) reported no difference in spatial suppression at high contrast among patients and healthy controls, but a significant increase of motion perception across all sizes in patients. The authors suggested that perhaps gain control abnormalities has masked the differences within the groups at high contrast (Foss-Feig et al., 2013, Katzner et al., 2011).

1.3.1.5 Recent work in migraine

There are some evidence suggesting that there is a link between migraine and cortical hyperexcitability (Aurora and Wilkinson, 2007). This would mean that psychophysical tasks should suggest weaker surround suppression in this condition. However, Battista et al. (2010), Battista et al. (2011) reported increase of motion and contrast suppression index in patients with migraine.

1.3.1.6 Discussion of psychophysical clinical studies

The previous sections explained some of the visual psychophysical work in different groups of patients. However, the results are complex and hard to interpret. It is important to emphasize that visual psychophysics have not been used as a method of diagnosis, but rather as a non-invasive way to understand more about the pathology of a patient's group. There are some studies however, that are questioning the presumed link between surround suppression and cortical inhibition. Blockade of GABA receptors in primate MT, did not cause a decrease in surround suppression (Liu and Pack, 2014). Another possible reason for discrepancies might be that perhaps surround suppression can be affected

by other neural factors (Rubin et al., 2014). A study done by Ozeki et al. (2009) used intracellular recordings in cat V1 and reported that the inhibition that neurons receive by the effect of surround stimuli is decreased and instead, suppression is mediated by termination of excitation and V1 is operating as an inhibition-stabilized network. Moreover, a lot of patients' groups in the mentioned studies were on medication which may cause changes in inhibitory processes and consequently in the suppression index.

1.4 Relevance to epilepsy

Given the impaired spatial suppression in the above special population, it is possible to speculate that perhaps similar impairment could be detected by visual psychophysics in epilepsy. The so-called "GABA-hypothesis" in different types of epilepsy suggests that a reduction of GABA-ergic inhibition allows epilepsy and an enhancement of GABAergic inhibition results in an antiepileptic effect (Calcagnotto et al., 2005, Bernard et al., 1999, De Deyn et al., 1990). If the effects in vision broadly classed as "surround suppression" are mediated by GABAergic mechanisms, despite the criticisms just noted, then the GABA-hypothesis in epilepsy implies that we might see abnormalities in visual surround suppression. We speculated that possible abnormalities in visual performance are more likely to be observed in genetic epilepsy or in occipital lobe epilepsy which is less common than other types of focal epilepsy, such as temporal lobe. In particular, cortical inhibition is believed to be a common deficit in a mouse model of human genetic epilepsy (Petrou and Reid, 2012). Even in the case of focal epilepsy, we might still see an effect on the visual performance if the focus is in another lobe. Because the inhibitory deficit might be widespread enough to be detected by the visual psychophysics. The overall cortical inhibition is more likely to be compromised in generalised epilepsy compared to focal epilepsy

where the affected area is only the focus of seizures, except in occipital lobe focal epilepsy. Furthermore, if the same class of interneuron that subserves surround suppression also stops seizures spreading, then failure in one role may predict failure in the other. In other words, we will take a far wider sample of seizure phenotypes, in order to examine visual deficits that arise from global deficits in inhibition.

As the review of the literature has shown, “visual surround suppression” is not a single phenomenon, so it is entirely possible that one type of so-called “visual surround suppression” would be altered in epilepsy while other types would not be. To maximise the chance of finding an effect, we have chosen two different tasks, one based on motion and one based on contrast, which have been both used previously with a range of clinical groups.

As reviewed above, previous studies have shown differences between control and patient populations in several different measures of visual surround suppression, although no one has yet examined these in epilepsy. However, as far as we are aware all these studies have only considered differences between these populations at a single point in time, even though many of the clinical conditions in question (for example schizophrenia, depression) are characterised by large fluctuations in severity. In this thesis, as well as considering differences between patient and control populations in epilepsy, I also examine within-subject fluctuations over time (longitudinal study). Moreover, I was interested in whether psychophysical results correlated with seizure timings and therefore, could be used as a way of monitoring and in particular predicting the likelihood of seizure occurrence as a non-invasive method at home.

1.5 The aims of this thesis

- To investigate whether visual psychophysics can be used as a potential tool to predict a seizure in patients with epilepsy. Three different paradigms of visual psychophysics which are believed to measure cortical inhibition were used, the motion discrimination, the contrast detection and the orientation discrimination tasks.
- To investigate whether these visual psychophysical tasks are correlated with each other and what is their relationship.
- To examine the differences in performance of patients with epilepsy and healthy controls.
- To explore the possibility of using visual psychophysics as a method of predicting seizures.

Chapter 2 Materials and methods

2.1 Ethics

2.1.1 Newcastle

Experimental procedures were approved by Newcastle and North Tyneside 1 Research Ethics Committee (reference number 09/H0906/90). Participants gave written informed consent and were paid a nominal fee for their participation.

2.1.2 India

The study proposal was submitted and approved by the Institutional Ethics Committee (IEC) of the INK Hospital.

2.2 Newcastle recruitment policies

2.2.1 Healthy participants

146 healthy volunteers with no visual or neurological problems (87 female; mean age: 36.6; range: 17.3-69.1) were recruited from Newcastle University data base of volunteer subjects. They were contacted by email or telephone by the researcher in order to set an appointment. All of the recruited healthy participants performed the motion discrimination task and from this population, 43 participants took part in a contrast detection task (34 female; mean age: 42.2; range: 19.4-74.2), and 7 (4 male; mean age=30.3; range=23.1-47.8) in an orientation discrimination task. Several took part in longitudinal studies, gathering repeated performance data on these tests over multiple days to weeks.

2.2.2 Patients with epilepsy

54 patients with confirmed epilepsy (30 male; mean age: 42.3; range: 17-82.33) were recruited by the researcher from Royal Victoria Infirmary's (RVI) epilepsy clinics, video-telemetry department, and a local epilepsy support group. Within

this population, 34 patients participated in a contrast detection task (18 female; mean age: 42.2; range: 21.7-82.3), and 2 patients (2 male; mean age: 55.8) in an orientation discrimination task. Twenty patients with epilepsy were recruited by the researcher for the longitudinal study, but four were unable to run the tests unaided, and so were excluded from further analysis. Therefore, 16 patients took part in the longitudinal studies. These patients were selected based on their high frequency of seizures, so that the chance of recording seizures at the time of running the tasks increases.

Information regarding each patient is provided in Appendix 2. A few patients with confirmed epilepsy were suspected to have non-epileptic seizures in addition to epileptic seizures. The exclusion criteria were: patients were under 18 years old, patients were suspected to only experience non-epileptic seizures, patients with significant visual impairment, and those with severe learning disability.

Patients were given instructions about the tasks and the research question, and were encouraged to ask questions. They could decide at that time or later whether or not to participate. If they were interested, an appointment was set in the RVI and they were compensated for their travel expenses. Longitudinal patients were given instructions while they were in-patients at the video telemetry department in RVI. Patients (sometimes with the help of a family member or an accompanying friend) filled out a questionnaire regarding concurrent health issues and current medication, seizure frequency, type of seizures and the first time they had a seizure, however they were not asked directly about a history of depression and anxiety. Patients' frequency of seizures was estimated in terms of the number of seizures per year, month, week or day (Appendix 2 and Appendix 6). This information was later used as a clinical marker of epilepsy severity. Most of the patients were unable to provide a precise

estimate of their number of seizures for different reasons, such as not keeping a record, not being aware of them, or not remembering. Specifically, there were 3 patients who were unable to give an estimate of their number of seizures. In these instances frequency of seizures was extracted from their records. The numbers of seizures reported were derived from the best knowledge of the patients, their witnesses, or what was recorded in their medical records and are indeed subject to uncertainty. Frequency of seizures could change in any patient and patients may have periods of remission or active spontaneous seizures for months or years. Therefore, we used the information that was the one most close in time to the time of participation in the study. The analysis of seizure frequency was collated blind to the results of their performance in the psychophysics tests.

Patients also completed an Addenbrooke's Cognitive Examination (ACE) test (Mioshi et al., 2006) which showed no difference in performance on the test between the groups of epilepsy. Patients with focal epilepsy with a history of generalised seizures (F^+, n = 19) have ACE = 90.5 +/- 6.2 (mean +/- std) with range of 72-96, patients with focal epilepsy without generalising seizures (F^-, n = 24) have ACE = 88.5 +/- 6.3 with range of 73-99 and patients with generalized genetic epilepsy (GGE, n = 11) have ACE = 92.0 +/- 4.1 with range of 85-100.

2.3 India recruitment policies

2.3.1 The rationale of this recruitment

Patient recruitment in Newcastle proved to be very slow, therefore patient and control recruitment was done as part of collaboration that was started between Institute of Neuroscience (IoN) in Newcastle and the Institute of Neurosciences Kolkata (INK) in India (INK; http://www.neurokolkata.org/). Patient recruitment was done by Dr. Jenny Read and collaborators in India (Dr. Ashish Datta, Dr. Rajib Samanta, Dr. Hrishikesh Kumar and Swagata Sen). Dr. Jenny Read trained MS.

Sen for around two weeks while she was conducting the test. After Dr. Read left India, recruitment and data collection continued for about six months. Based on the preliminary data collection from around 20 patients and 10 controls that we had acquired in India at the time, a power calculation using GPower statistical tool (Faul et al., 2007) suggested that with power of 0.08, we should aim to gather data from a further 36 patients and 15 controls.

2.3.2 Healthy participants

25 age and sex matched healthy controls to patients (17 male; average age: 30.65; range: 18.16-60.5) were recruited from staff of INK or the accompanying family members. Results of the contrast detection task of one of the control participants (KC43) was missing at the time of analysis.

2.3.3 Patients with epilepsy

56 patients with confirmed epilepsy (37 male; average age: 33.7; range: 17.9-64.6) were recruited based on their medical history and neurological examination from epilepsy clinics of the INK. Table 2 displays a full description of information regarding each patient. Results of the motion discrimination task of one of the controls in India (KP55) was missing at the time of analysis. The exclusion criteria were: patients were under 18 years old, patients who had epileptic seizures 24 hours prior to the test, patients who were suspected to only experience non-epileptic seizures, patients with significant visual impairment, and those with cognitive impairment sufficient to prevent them from providing informed consent.

Patients were given instructions about the tasks and the research objectives, and were encouraged to ask questions. However, they were not asked about any history of depression or anxiety. The information regarding anti-epileptic drugs that were recorded for Indian patients was assessed by an independent

neurological clinician and was concluded that there is no significant difference between the prescribed drugs in Newcastle and India.

2.3.4 Experimental protocol

Patients were approached by the India based investigator (Ms. Swagata Sen) during their attendance at a routine out-patient appointment. They were given instructions prior to recruitment. A convenient time was arranged and possible questions were answered. The same protocol as in Newcastle was followed for motion direction and contrast discrimination tasks in India. An identical equipment to what was used in Newcastle was shipped to India (P1210 Compaq CRT (Cathode Ray Tube), Table 2.1).

2.4 Visual psychophysics

Before the invention of powerful techniques using computers, a common way to estimate a threshold in a contrast detection task was to display a stimulus on an oscilloscope and ask observers to manually change the contrast until the stimulus was “just noticeable” against the background (referred to as the method of adjustment) (Kingdom and Prins, 2010). However, nowadays “staircase methods” are mainly used which typically start with a high intensity, and the intensity of successive trials is then set based on the previous answer of the observer. The intensity is decreased until the observer makes a mistake, after which the intensity is increased in the subsequent trial. This will make an imaginary staircase that will “home in”, over relatively fewer trials, on the intensity that is close to the observer’s threshold (Pelli and Farell, 2010, Watson and Pelli, 1983, King-Smith et al., 1994, Treutwein, 1995).

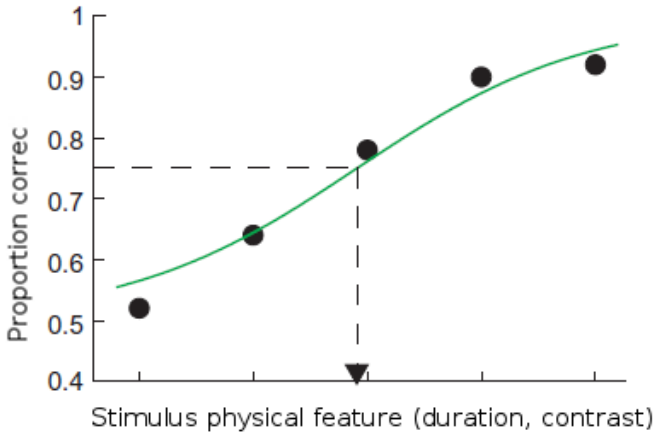


Figure 2.1. An example of a psychometric function adopted from Kingdom and Prins (2010) showing data fitted with a logistic function which shows the threshold, defined as the stimulus value at which the performance gets 0.75.

2.5 Apparatus

Stimuli were created in MatLab (www.mathworks.com) with the Psychophysics toolbox called Psychtoolbox which interfaces between MatLab and the computer hardware (Brainard, 1997, Pelli, 1997). Experiments were shown for all control subjects and 31 of patients with epilepsy on a 22inch P1210 Compaq CRT (Cathode Ray Tube) with 800×600 pixels resolution and frame rate of 160Hz. A DATAPixx Lite visual stimulator from VPixx Technologies (http://www.vpixx.com/products/visual-stimulators/datapixx-lite.html) was used to generate the visual stimuli with 12-bit pixel depth. A RESPONSEPixx tabletop (http://www.vpixx.com/products/response-boxes/tabletop.html) was used to record subject responses.

For the purpose of testing subjects on a longitudinal basis, Samsung (model: XE700T1C) and Acer (model: TravelMate X313-M) tablets were used for 23 patients (Table 2.1).

Table 2.1. Technical description of devices used to collect subjects' responses

P1210 Compaq CRT (Cathode Ray Tube)	Samsung XE700T1C	Acer Travel Mate X313-M
Screen: 22 inch	Screen: 11.6" touch screen	Screen: 11.6" touch screen
Resolution: 800×600	Resolution: 1920 x 1080	Resolution: 1366 x 768
frame rate: 160 Hz	Frame rate: fps	Frame rate: 17.5 fps
Processor: Core i3, 3.06 GHz	Processor: Core i5, 1.7 GHz	Processor: Core i5, 1.5 GHz
RAM: 4GB	RAM: 4GB	RAM: 4GB
-	Storage Capacity: 128 GB SSD	Storage Capacity: 120 GB SSD
Windows Vista	Windows 8 Pro 64-bit	Windows 8 Pro 64-bit

Gamma correction was applied to perform grayscale calibration and linearization on monitors. This was necessary to precisely control the luminance on the screens. Each pixel on a monitor has a value between 0 (darkest) to 255 (brightest). It is important that the same amount of increase in the pixel value results in the same increase in luminance emitted from the monitor, so that the response is linear. In most cases CRTs have a nonlinear response to input signal.

The luminance is generally modelled as a power function of pixel value with an exponent called gamma (γ).

$$Luminance = L_{min} + (L_{max} - L_{min}) * [\frac{pixel\ value - black}{white - black}]^{\gamma}$$

Equation 2.1. Gamma is the power describing how fast the luminance rises as a function of pixel value. L_{min} and L_{max} represent luminance of black and white, respectively. Linearity is the case gamma=1.

Gamma (γ) can be calculated by making a table of pixel values versus luminance for the uncorrected monitor and then fitting a function in the form of Equation 2.1, where L_{min} is the measured luminance when pixel value is set to black or 0 and L_{max} is when pixel value is set to white or 255.

To correct the nonlinearity, gamma correction applies a transformation to the graphic card (Cao et al., 2014, Eriksson et al., 1998) . Here, gamma was measured for the uncorrected monitor. Then the measured gamma was sent to the Psychtoolbox interface, so that in practice gamma was corrected to 1.

Code displaying the drifting Gabor patch was programmed in MatLab using the Psychophysics Toolbox Version 3 (PTB-3) (Brainard, 1997, Kleiner et al., 2007, Pelli, 1997). For participants using the CRT, viewing was binocular at 100cm in a dimly-lit room (luminance reflected by a white sheet of paper in the room was about 0.8cd/m^2). Participants using tablets were instructed to perform tests in a dimly-lit room at distance set to 60cm. They were helped by the experimenter to find a suitable location.

In order to test the effect of room ambient lighting on the measured thresholds, one control subject repeated motion discrimination task twice in three different ambient lighting conditions. Ambient lighting was measured by pointing a photometer towards the direction of the computer in a room with no source of light. A one-way ANOVA test was performed on the average of each condition (Table 2.2). Anova test showed no significant difference between groups in small, large duration thresholds and motion suppression index (For small duration thresholds: P=0.24, F=3.18; large duration thresholds: P=0.56, F=3.18; motion suppression index: P=0.478, F=1.09). However this difference might be due to within- and between-subject variabilities (Read et al., 2015).

All room lighting measurements and gamma correction were performed using a Minolta photometer model Luminance Meter LS-100.

Table 2.2. Different measurements of ambient lighting and their corresponding duration thresholds and suppression index of one healthy subject

Measured lighting	Average of two small duration thresholds	Average of two large duration thresholds	Average of two motion suppression indices
0.37 cd/m^2	37.8345	149.8025	0.5994
1.54 cd/m^2	25.633	132.269	0.7127
31.55 cd/m^2	32.984	107.514	0.4918

2.6 Motion direction discrimination task

This protocol followed that described by Tadin et al. (2006), Tadin et al. (2003). Before each trial, there was 500ms during which a small fixation cross appeared and disappeared with a Gaussian temporal function with a standard deviation of 80ms, to encourage participants to look at the centre. Then there was a 700ms interval during which the stimulus appeared and disappeared, with a Gaussian temporal function. The stimulus was a standard drifting Gabor patch, presented using CreateProceduralGabor function of Psychtoolbox-3 (Brainard, 1997, Pelli, 1997). The stimulus always had its peak contrast halfway through the 700ms interval. 700ms was chosen as being long compared to the duration thresholds we expected, so that the temporal Gaussian would have time to rise smoothly from zero contrast and return to zero again within this window. A schematic of stimulus is shown in Figure 2.2. Gabor patches are commonly used in vision studies because they are localised in both frequency space and visual space. They are sinusoidal gratings within a temporal and spatial Gaussian window. Here different stimulus durations of Gabor patch was controlled by an adaptive staircase procedure. Participants were asked to distinguish the direction of motion of the drifting Gabor by pressing the left or right buttons on the

ResponsePixx box for the CRT, or touching the left or right side of the screen for the tablets (Figure 2.3).

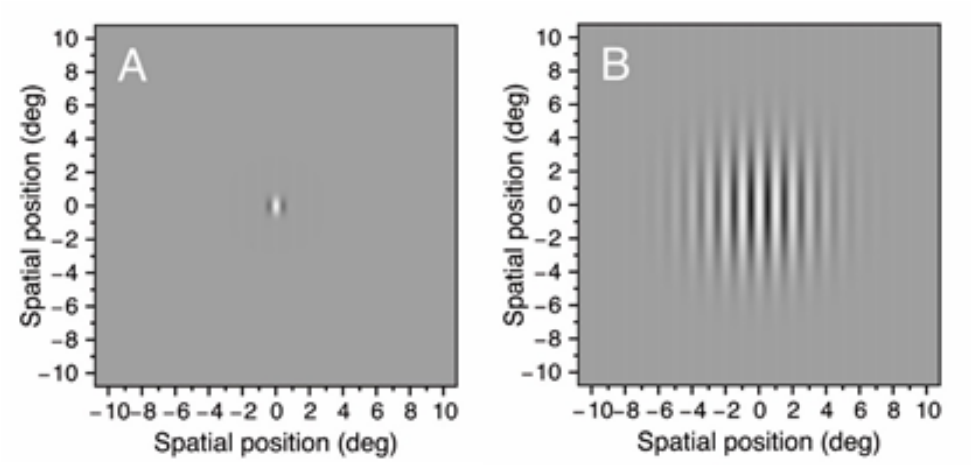


Figure 2.2. Schematic illustration of the motion discrimination task. A: Small stimulus with size $2\sigma=0.7^{o}$, B: large stimulus with size $2\sigma=5^{o}$. Stimulus was standard Gabor patch, a drifting vertical sine grating windowed by a Gaussian spatial envelope. Stimulus direction was rightward or leftward, and the task was to identify this moving direction.

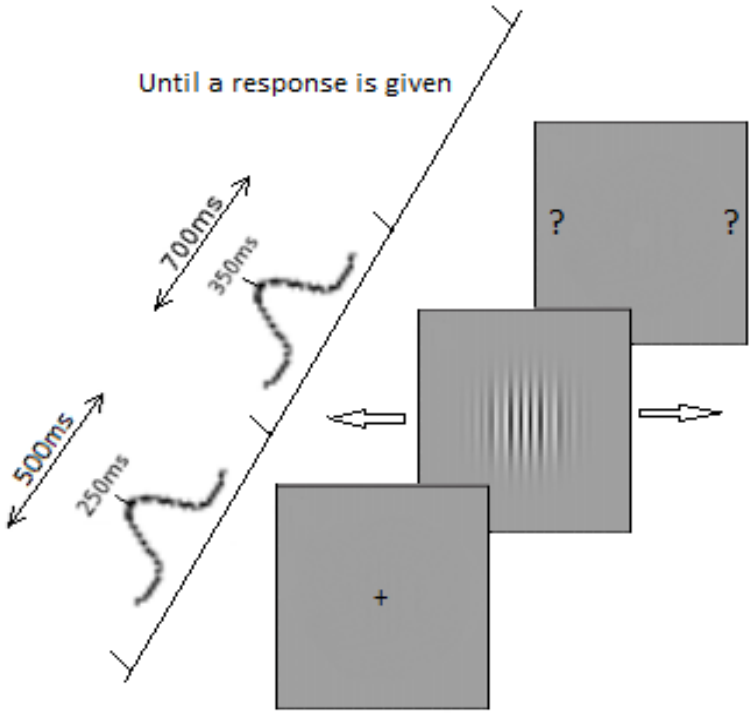


Figure 2.3. A schematic of the motion discrimination task. The stimulus appears and disappears, with a Gaussian temporal function**.**

The envelope was stationary on the screen, but the carrier sine wave moved horizontally at constant speed. The carrier spatial and temporal frequencies were 1 cycle per degree and 2 cycles per second (Hz) respectively, resulting in a speed of 2 degrees per second. Stimuli appeared within a temporal Gaussian envelope, so the stimulus contrast rose up from zero to a peak value which is the "Contrast" and then down again. Two different stimulus contrasts were used: "high contrast" (peak contrast = 92%) and "low contrast" (peak contrast = 2.8%). "Duration" of the stimulus was defined as twice the temporal Gaussian standard deviation, 2τ.

Each trial was set to last 10τ, with the peak contrast occurring halfway through. This means that the total time taken by each trial depends on the value of τ. This was done so that the temporal Gaussian was never truncated; stimuli always began with zero contrast at the beginning of a trial rather than appearing abruptly. τ was constrained to lie in the range 10-1000ms if the staircase wanted to choose values outside this range. Size of the stimulus was defined as twice the spatial standard deviation of the Gaussian envelope (2σ), and used two different sizes, small stimuli with size of $2\sigma=0.7^{o}$ and large stimuli with the size of $2\sigma=5^{o}$. Task difficulty was modulated by altering stimulus duration.

2.6.1 Experimental protocol

Patients were given instructions (Appendix 4) about the experiment and research question prior to recruitment, and were encouraged to ask questions. Control participants completed the entire task at one visit. Patients who did the tasks only once completed the tasks in a single appointment; however experiments were repeated multiple times over a longer period of time for longitudinal patients. The length of participation in the study was dependent on the number of seizures they experienced. They were encouraged to carry on till 2 or more than 2 seizures were reported, however in some cases no seizure was

reported. All participants could ask for a break within each trial and also in between the tasks. The overall time to complete experiment was around 20 minutes for controls and single visit patients, but for longitudinal patients this time was shortened to 10 minutes by reducing the number of repeat trials in the test.

2.6.2 Psychophysical task

"Surround suppression index" was introduced by Tadin et al. (2006) to measure the power of centre-surround suppression at high contrast. This term is defined as the logarithm of the ratio of the duration thresholds T for large and small stimuli:

$$\text{Motion suppression index} = \log_{10}\left(\mathrm{T}_{\mathrm{large}} - \mathrm{T}_{\mathrm{small}}\right) = \log_{10}\left(\frac{\mathrm{T}_{\mathrm{large}}}{\mathrm{T}_{\mathrm{small}}}\right)$$

Equation 2.2. Motion suppression index was introduced, in order to quantify the amount of suppression. Duration thresholds of large and small stimuli are denoted by T.

A positive motion suppression index shows that the large duration threshold is bigger than small duration threshold (shorter duration thresholds for small stimuli), whereas a negative index shows shorter duration thresholds for larger stimuli, which is indicative of spatial summation (Anderson & Burr, 1991). A motion suppression index of one show equal durations. Equation 2.2 can also be used in low contrast in which case it is called "motion summation index" and is usually negative.

2.7 Contrast detection task

The stimuli is adapted from Serrano-Pedraza et al. (2012), which is a combination of what Yoon et al. (2010), Cannon and Fullenkamp (1991), and Petrov et al. (2005) have used. An example of the stimulus is shown in Figure 2.4. There is a large sinusoidal luminance grating at the background with spatial frequency of 1.1 cycles per degree, contrast of 25%, diameter of 18°, and orientation of $\pm 45^{\circ}$ to the vertical. Four circular holes located on cardinal directions and centred on an eccentricity of 4.2° with diameter of 2.3° were cut out from the large background grating. On each trial one of these holes (target) was filled with the stimulus which was a sinusoidal grating with the same diameter as the hole and the same spatial frequency as the large background grating. The stimulus was presented within a temporal Gaussian window with standard deviation of 50ms. All gratings and holes were presented within a 10^{th}-order Butterworth window in order to get smooth edges. At the start of each trial, a rotating fixation cross was shown at the centre of the screen for 500ms. A schematic of the process of presenting the stimulus is shown in Figure 2.5. The task was to detect the position of the target by choosing one of four buttons on the ResponsePixx box (for those who used the CRT), or touching the area surrounded by the target. This location and the orientation of the background were changed randomly on each trial. The target could have two orientations: parallel or orthogonal to surrounding background. The difficulty of the task was modulated by changing the contrast of target, which is the peak contrast within the temporal Gaussian window.

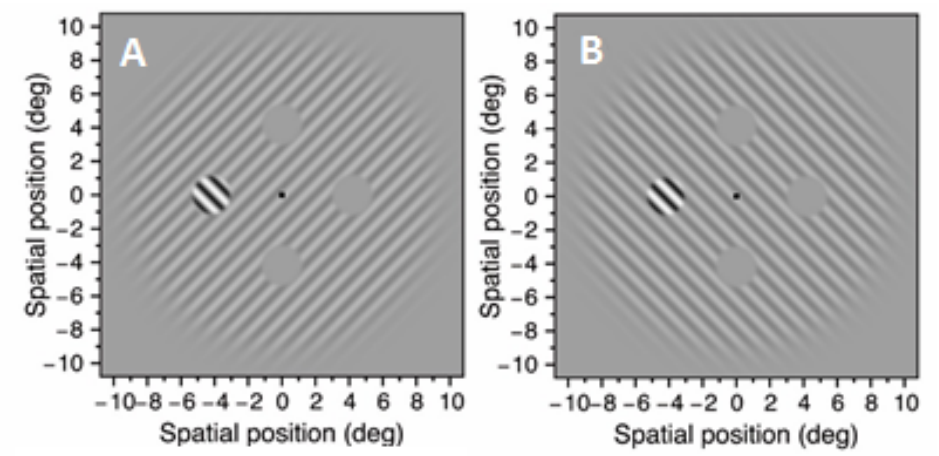


Figure 2.4. Schematic illustration of the contrast detection task. A: Stimulus with an orthogonal surround. B: Stimulus with a parallel surround. Task was to detect the location of the target appearing in one of the four holes in the periphery.

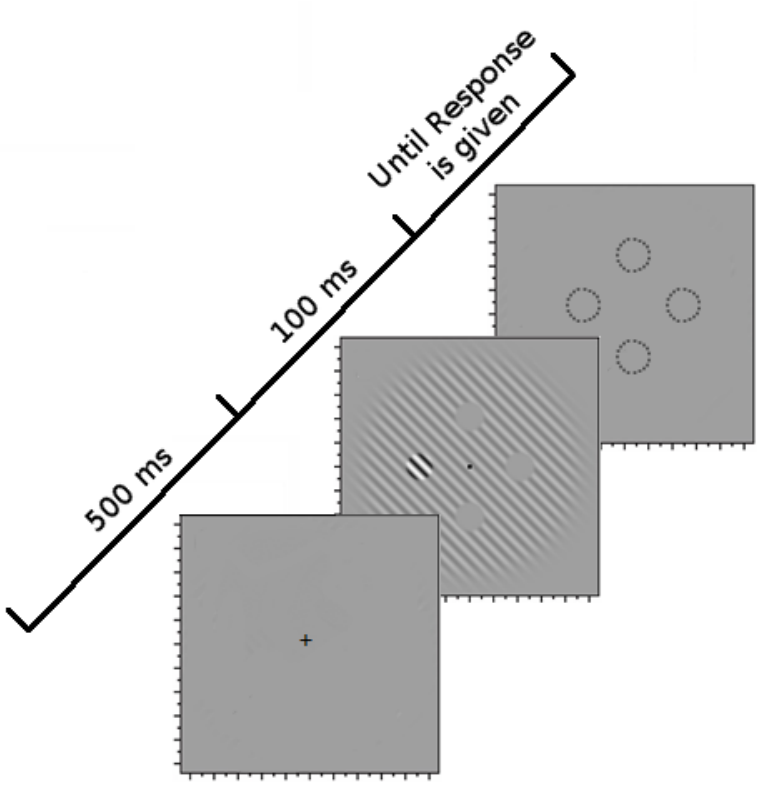


Figure 2.5. A schematic of the contrast detection task.

2.7.1 Experimental protocols

The contrast detection task was typically started after the motion discrimination task. For participants using tablets, the order of tests was randomly switched. The overall time to complete this task was around 10 minutes for controls and single visit patients, but for longitudinal patients this time was shortened to 5 minutes.

2.7.2 Psychophysical task

A "Contrast suppression index" analogous to the motion suppression index was defined to measure the strength of centre-surround suppression for parallel and orthogonal conditions. This term was defined as the logarithm of the ratio of the contrast thresholds C for parallel and orthogonal conditions:

$$\text{Contrast suppression index} = \log_{10}\left(\mathrm{C}_{\text{parallel}} - \mathrm{C}_{\text{Orthogonal}}\right) = \log_{10}\left(\frac{\mathrm{C}_{\text{parallel}}}{\mathrm{C}_{\text{Orthogonal}}}\right)$$

Equation 2.3. Contrast suppression index was introduced to quantify the amonut of suppression. Contrast thresholds of parallel and orthogonal stimuli are denoted by C.

In this task, contrast thresholds for target surrounded by a grating of the same orientation (parallel) are usually higher than for those with an orthogonal surrounding grating (Ejima and Takahashi, 1985, Lev and Polat, 2011, Petrov et al., 2005, Polat and Sagi, 1993, Serrano-Pedraza et al., 2012, Snowden and Hammett, 1998b, Xing and Heeger, 2000, Yu and Levi, 2000).

2.8 Orientation discrimination task

This experiment was adopted from Edden et al. (2009b). An example of this experiment is seen in Figure 2.6. On each trial two circular gratings with two

different orientations were shown on the tablet screen. The mean orientation of the gratings was set to 45°.Participants were asked to determine if the second grating was tilted clockwise or counter clockwise relative to the first. Participants were instructed to give their responses by touching the right or left side of the screen.

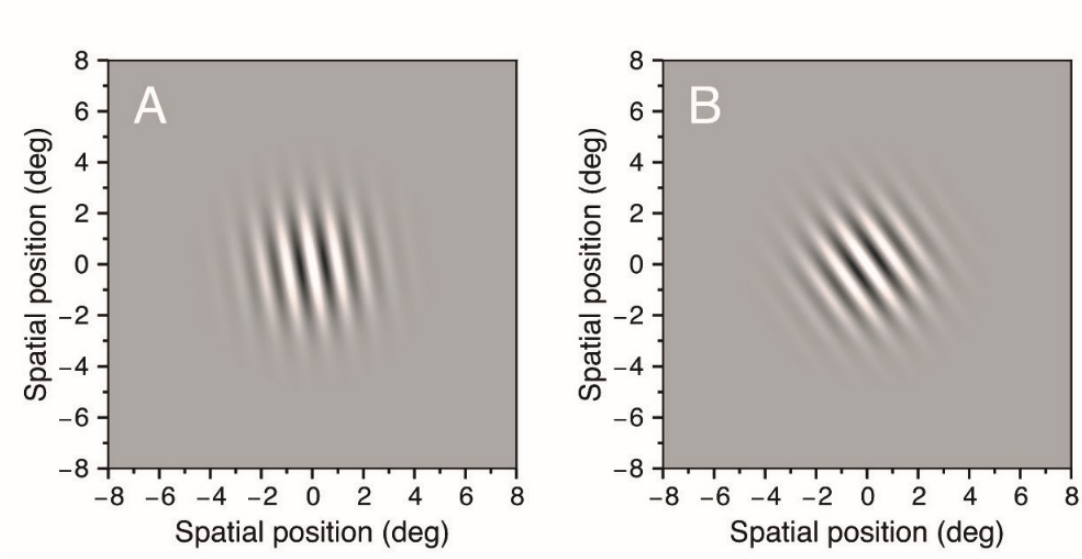


Figure 2.6. Schematic illustration of the orientation discrimination task. The grating has frequency of 0.02 cycle per degree and size of 1.47 degree. A is a grating with rotation of 10 and B with 35 degrees.

2.8.1 Experimental protocol

On each trial two circular gratings with diameter of 1.47° and spatial frequency of 0.02 cycle/degree were shown for 350ms on the tablet screen.

2.9 Data analysis

In order to analyze the psychophysical data, programmes were run in the MATLAB environment. For statistical analysis Microsoft office 2013 (such as Excel), MATLAB built-in functions and IBM SPSS (Multiple regression analysis, Analysis of covariance, Analysis of variance, non-parametric tests) were used. The specific tool will be mentioned as I present the results.

Some of the data throughout this thesis will be presented as a boxplot (shown in Figure 2.7).

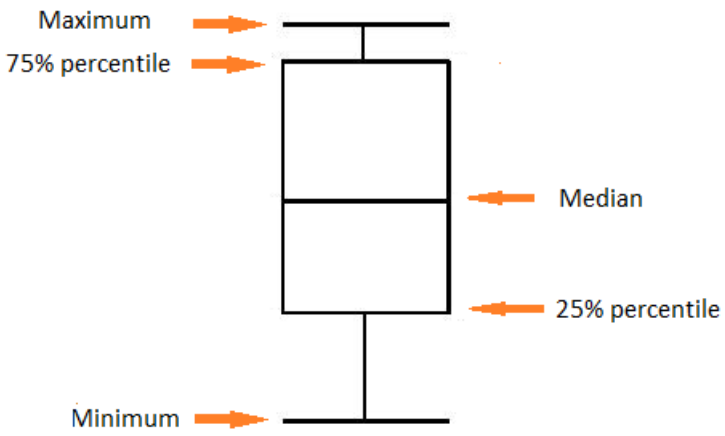


Figure 2.7. The distribution of data can be displayed as a boxplot based on the minimum, 75% quartile, median, 25% quartile and maximum.

Boxplots provide a visualised way of demonstrating the distribution of data using z-scores. By definition z-score indicates how many standard deviations a data point is away from the mean.

$$z = \frac{SI - \mu}{\sigma}$$

Equation 2.4. Calculating the z-score of suppression indices (SI) of each individual where μ is the mean and σ is the standard deviation.

These numbers can then be plotted in boxplots as bee swarm plots (plot spread points) using MatLab to present the spread of data points, outliers and the median in each group.

2.9.1 Measurement of estimate of motion and contrast threshold

Evaluating psychophysical thresholds can be achieved using adaptive or non-adaptive methods (King-Smith et al., 1994). In adaptive methods, the intensity of each trial depends on the previous response (Falmagne, 1986). A correct response makes the next intensity get higher, while a wrong response results in a reduced intensity. When there is high uncertainty about the threshold, adaptive methods are recommended (King-Smith et al., 1994), as they are designed to present stimuli with most intensities close to threshold (Watson and Fitzhugh, 1990, Treutwein, 1995).

Adaptive methods can be in different types, such as a simple staircase (Cornsweet, 1962) in which stimulus intensities are increased or reduced in fixed steps, or trials defined in set blocks of intensity (Taylor and Creelman, 1967, Findlay, 1978), or maximum likelihood (Hall, 1968, Pentland, 1980, Watson and Pelli, 1983) in which after each trial the most likely threshold is estimated and used as the intensity for the next trial.

Maximum likelihood offers high efficiency among other types of adaptive threshold methods, and the final threshold is the most likely estimate of threshold after the last trial (King-Smith et al., 1994). The best known maximum likelihood method is the Quest method (Watson and Pelli, 1983). In Quest, the experimenter`s knowledge about the probability of different threshold values is taken into account. This is known as the initial probability density function (pdf), and the mode of this pdf is chosen as the first stimulus intensity. Based on the answer to the first stimulus, next stimulus intensity is chosen. Watson and Pelli

(1983) showed that the pdf after trial i, $q_i(T)$, is the product of previous pdf with the corresponding likelihood function using Bayes' theorem. Given T as the log threshold:

$$q_i(T) = p(r_i, x_i, T) q_{i-1}(T)$$

Equation 2.5. $q_i(T)$ is the pdf after trial i, $p(r_i, x_i, T)$ is the likelihood function and the probability that the subject gives response r (1 for a correct response and 0 for an incorrect response) to a stimulus with intensity x_i, and $q_{i-1}(T)$ is the pdf of the previous response.

While in the original paper of Watson and Pelli (1983) method of choosing the stimulus intensity of each trial was preferred to be the mode of the pdf, here mean of the pdf was used (ZEST method). ZEST is believed to be more efficient and precise for finding the threshold (King-Smith et al., 1994, Alcala-Quintana and Garcia-Perez, 2004).

Here duration and contrast thresholds were measured using 2 or 3 randomly interleaved adaptive Bayesian staircases (Treutwein, 1995) with each containing 50 or 30 trials. In the case of longitudinal study, 30 trials with 2 staircases were used to reduce the time of experiment. The code for this section was written in MatLab by a previous post doctorate research associate of Dr. Read (Dr. Ignacio Serrano-Pedraza). I used this code and made occasional changes at different stages of the study.

Psychometric function (ψ) refers to the probability of success against the stimulus level, here the stimulus duration (Treutwein, 1995, Luce and Krumhansl, 1988, Baird and Noma, 1978). It is also important to account for the events that are higher than the threshold, but the participant fails to notice them (lapse rate or p_l) and events that are below the threshold, but the participant

answers correctly (guess rate or p_g). Considering all these parameters a psychometric function can be estimated using (Whichmann and Hill, 2001):

$$\psi = p_g + \left(1 - p_g - p_l\right) * F(x)$$

Equation 2.6. Psychometric function (ψ). p_g is the guess rate, p_l is the lapse rate and $F(x)$ is a choice of sigmoid function for the stimulus intensity x.

This psychometric function was fitted to all trials collected for each participant to estimate duration thresholds (Figure 2.8). To model $F(x)$, a logistic function was used to define the probability that each participant correctly discriminates the direction of the motion for stimulus duration of τ (Equation 2.7) in motion discrimination task and the correct contrast of stimulus τ for the contrast detection task.

$$F(\tau) = \frac{1}{[1 + \exp\big(\mathrm{b}(\mathrm{a} - \ln\tau)\big)]}$$

Equation 2.7. Logistic psychometric function. τ is the stimulus duration. This function has two parameters. Parameter "a" defines how steeply the function rises as it passes through its midpoint, and parameter "b" determines the intercept of the function. Here "b" was set to 10, and duration threshold was estimated by calculating parameter "a".

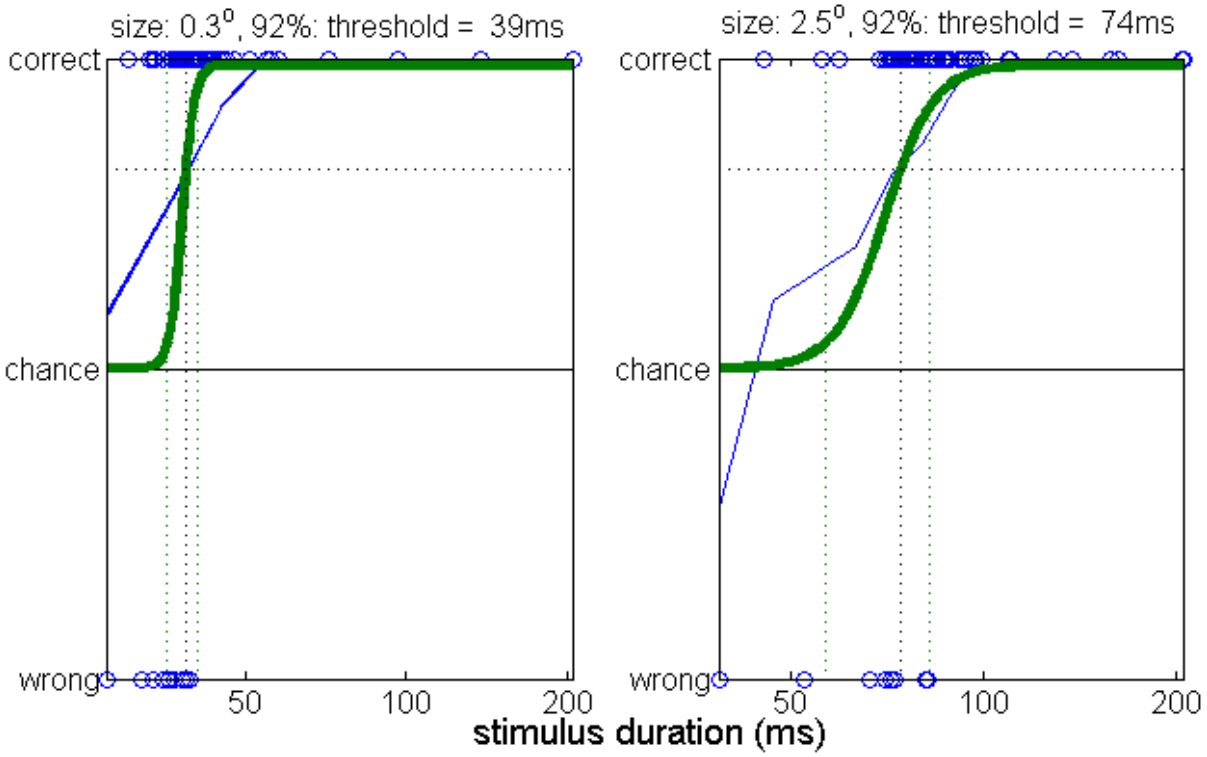


Figure 2.8. Schematic example of obtaining participants` responses either correct or wrong (in blue circles) to motion discrimination task in different stimulus durations at three different conditions: correct, chance (50%), and wrong. In order to find the overall trend of data, moving average of data points was plotted in solid blue line. Green solid line is the fitted psychometric function.

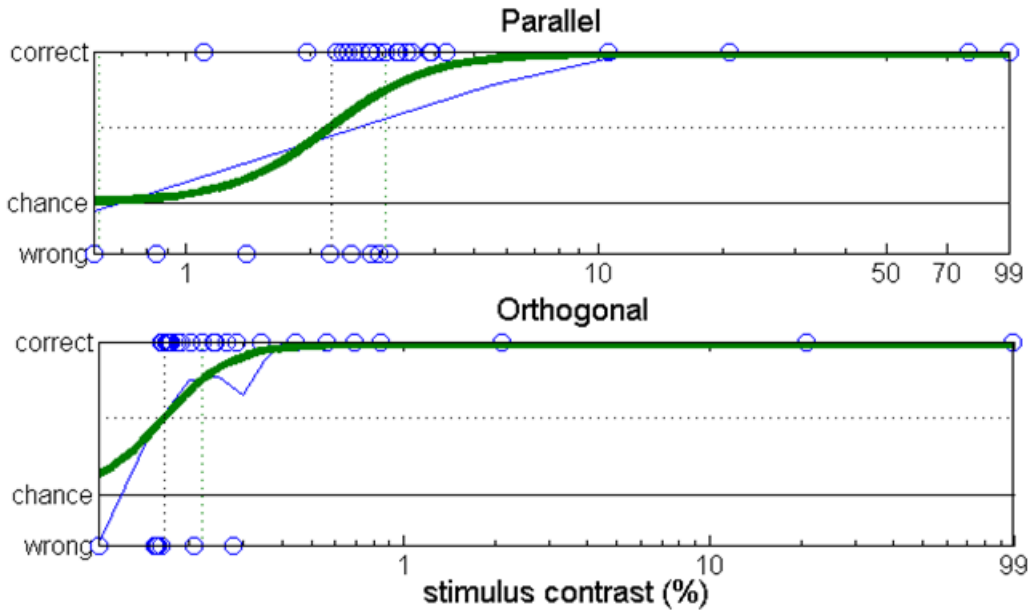


Figure 2.9. Schematic illustration of obtaining participants` responses (in blue circles) to contrast detection task in different stimulus contrasts at three different conditions: correct, chance (25%), and wrong. The blue solid line is the moving average of all correct and wrong responses for each stimulus contrasts. Green solid line is the fitted psychometric function.

With substitution of $F(\tau)$ in Equation 2.8:

$$\psi(\tau) = p_g + \frac{1 - p_g - p_l}{1 + \exp\big(\mathrm{b}(\mathrm{a} - \ln\tau)\big)}$$

Equation 2.8. A logistic psyhometric function where p_g is the guess rate, p_l is the lapse rate, The initial estimate of a and b were set to mean log of stimulus intensity and 10, respectively. For motion discrimination task p_g was set to 50% or 0.5 since we used a 2-alternative paradigm. For contrast detection task p_g was 25% or 0.25 since we used a 4-alternative paradigm. The lapse rate p_l was set to 0.01 for both tasks.

Duration threshold θ was defined as the minimum time that each participant needed to correctly identify the direction of the moving stimuli on 82% of trials. The 82% value is the value that was used in Tadin et al. (2003) and Watson and

Pelli (1983) (From equation 13 page 116). Likewise, contrast threshold θ was defined as the minimum contrast that each participant needed to correctly detect the contrast of the target stimuli on 62.5% of time. The 62.5% value was chosen as it is half way from chance (25%) to perfect (100%).

If $\psi(\tau)$ = 82% or 62.5 % = t, then:

$$t = p_g + \frac{1 - p_g - p_l}{1 + \exp\big(\mathrm{b}(\mathrm{a} - \ln\theta)\big)}$$

Equation 2.9.

Therefore:

$$b(a - ln\theta) = \ln[\frac{1 - p_g - p_l}{t - p_g}]$$

Equation 2.10.

To estimate the value of threshold (θ), MatLab function fminsearch was used to determine the amount of "a" which maximizes the likelihood of a correct response (Read et al., 2015).

2.9.2 Measurement of confidence intervals- bootstrap resampling

Bootstrap resampling was used to extract 95% confidence intervals for the fitted thresholds. 10,000 resampled data with replacement from the total number of trials was generated. The threshold θ was then fitted to this new data set and 95% confidence interval on θ was extracted from 2.5% and 97.5% percentiles in the resampled fits.

2.9.3 Measurement of estimate of orientation threshold

Orientation discrimination thresholds were measured using Quest toolbox from MatLab (Quest) which implements Quest Bayesian (Watson and Pelli, 1983). For the orientation discrimination task, the same staircase stimulus selection was used, however a different approach for estimating the threshold was used (Quest). I wrote the entire code in MatLab as a pilot study.

In order to use the toolbox, first a structure with necessary information to create a Weibull psychometric function (Equation 2.11) was created using QuestCreate function.

$$pThreshold = p_l * p_g + (1 - p_l) * (1 - (1 - p_g) * e^{-10^{\beta*(x-xThreshold)}})$$

Equation 2.11. Weibull distribution

The Weibull parameters were set to the following: δ = 0.01 (lapse rate), p_g= 0.5 (chance rate), β = 3.5. Then, using this prior knowledge a number of trials were shown, and the observer`s response and the actual intensity were reported to another function (QuestUpdate). Information was saved in a structure and eventually at the end of the trials, Quest provided a final threshold estimate (using QuestMean and QuestSd) which was the mean and standard deviation of the pdf (Farell and Pelli, 1999, Watson and Pelli, 1983).

Chapter 3 Relationship between different psychophysical measures of surround suppression

3.1 Introduction

Psychophysical properties of surround suppression have been widely studied for several decades (Barlow and Mollon, 1982). These studies have used several forms of psychophysics to measure different thresholds such as contrast, duration, and orientation. Fascinating findings such as longer duration of time needed to perceive the direction of a large moving stimulus in compare to a smaller size (Tadin et al., 2003), or the decreased perceived contrast of a stimulus surrounded by another stimulus (Andriessen and Bouma, 1976, Cannon and Fullenkamp, 1991, Petrov et al., 2005, Snowden and Hammett, 1998a), are believed to be instances of psychophysical surround suppression. These findings are thought to be the perceptual correlate of inhibitory neuronal mechanisms in visual cortex (Tadin et al., 2003).

The apparent psychophysical measures of surround suppression are linked to different parts of visual cortex. For example, discrimination of direction of a drifting grating is attributed to surround suppression processing in V5 (MT) (Tadin et al., 2003), or contrast detection of a visual stimulus surrounded by a different stimulus is attributed to surround suppression in V1 (Zenger-Landolt and Heeger, 2003). While a lot of studies have used these psychophysical phenomena as a way of understanding the underlying pathology of different clinical conditions, such as schizophrenia (Yoon et al., 2010, Yoon et al., 2009, Chen et al., 2008, Robol et al., 2013, Serrano-Pedraza et al., 2014, Tibber et al., 2013, Yang et al., 2013a), autism (Flevaris and Murray, 2014, Foss-Feig et al., 2013, Koldewyn et al., 2010), and migraine (Battista et al., 2010, Battista et al., 2011), a number of them have found conflicting results. For example, Tadin et

al. (2006) found weakened centre-surround interactions in patients with schizophrenia, although Chen et al. (2008) reported increased surround suppression in patients with schizophrenia relative to matched controls. As Tibber et al. (2013) discussed, the problem lies in the fact that most of these studies usually use different psychophysical tests and diverse patients groups. In fact, one study by Yang et al. (2013a) used a similar methodology and patient group to test psychophysical thresholds on luminance, contrast, orientation, size and motion, and surprisingly only found decreased contrast surround suppression in the patient group compared to controls, suggesting no significant correlation between different measures of surround suppression in schizophrenia. The same group tested patients with bipolar disorder across similar visual tasks (Yang et al., 2013b), and found no significant difference in any of the psychophysical contextual tasks among patients and controls.

Psychophysical tasks have also been investigated to understand visual processing in senescence (Betts et al., 2009, Betts et al., 2005, Betts et al., 2012). While there is a broad age-related decrease in surround inhibition strength, studies done by Karas and McKendrick have shown that perceptual centre-surround inhibition of contrast is greater for older adults (61-84 years) than for younger people (18-33 years) (Karas and McKendrick, 2011, Karas and McKendrick, 2009, Karas and McKendrick, 2012, Karas and McKendrick, 2015).

The main question here is whether these different psychophysical measures reflect a single property of visual cortex, or each is an assessment of inhibition related to different areas of the visual cortex. Differences between patients and healthy control groups have been linked to altered GABA-ergic inhibition (Yoon et al., 2010, Tadin et al., 2006, Betts et al., 2005). One such patient groups with altered GABAergic inhibition includes people with epilepsy (Bromfield et al., 2006, Calcagnotto et al., 2005). The seizure onset might be within a distinct

location of the cortex. However, the activity can spread to engage other areas, and this is thought to reflect the quality of inhibitory restraint shown in these secondary territories (Trevelyan et al., 2006, Schevon et al., 2012, Trevelyan and Schevon, 2012). Patients with epilepsy can be diagnosed with focal seizures (within a discrete location of the cortex) or generalised seizures. An interesting possibility is that visual psychophysics may provide a way of assessing the inhibitory restraint mechanism, even in patients with epilepsy arising outside the visual cortex. On the other hand, if changes in GABA concentration occur independently between different regions of cortex, then different metrics of psychophysical surround suppression could potentially yield different results, which may be a possible cause of discrepancies in literature. There is no published study at this time about measures of surround suppression in epilepsy and visual psychophysics in the literature. I will show results of patients and healthy control groups in chapter 4.

In this chapter, I will discuss the relationship between motion and contrast suppression indices in a group of 36 healthy volunteer subjects (10 male; mean age: 42.3; range: 19.4-69.1), first to provide a benchmark for comparison with data from patients with epilepsy, which will be described in subsequent chapters. Participants had normal, or corrected to normal, visual acuity. They were recruited from Newcastle University data base of volunteer participants. This is a sub-section of the whole control population, as only thirty six control participants completed both direction discrimination and contrast detection task at the same visit and on the same equipment.

3.2 Results

3.2.1 Longer duration thresholds for large grating in high contrast, but shorter in low contrast

Duration thresholds were measured from 36 healthy control participants. Figure 3.1 shows a plot of duration thresholds on the motion discrimination task as a function of age. The top panels in Figure 3.1 show thresholds for high contrast stimuli; the bottom panels of Figure 3.1 (C-D) for low contrast stimuli. In high contrast, duration thresholds were longer for large stimuli than for small, meaning that it took longer time for participants to discriminate the moving direction of the stimulus when it is larger. This was reversed for low contrast stimuli, where participants showed longer duration thresholds for small stimulus, which means that shorter duration of time was needed to accurately perceive the large stimulus. Duration thresholds significantly increased with age in small high contrast stimuli ($p=0.02$, Figure 3.1 B) and in small low contrast stimuli ($p=0.0009$, Figure 3.1 D).

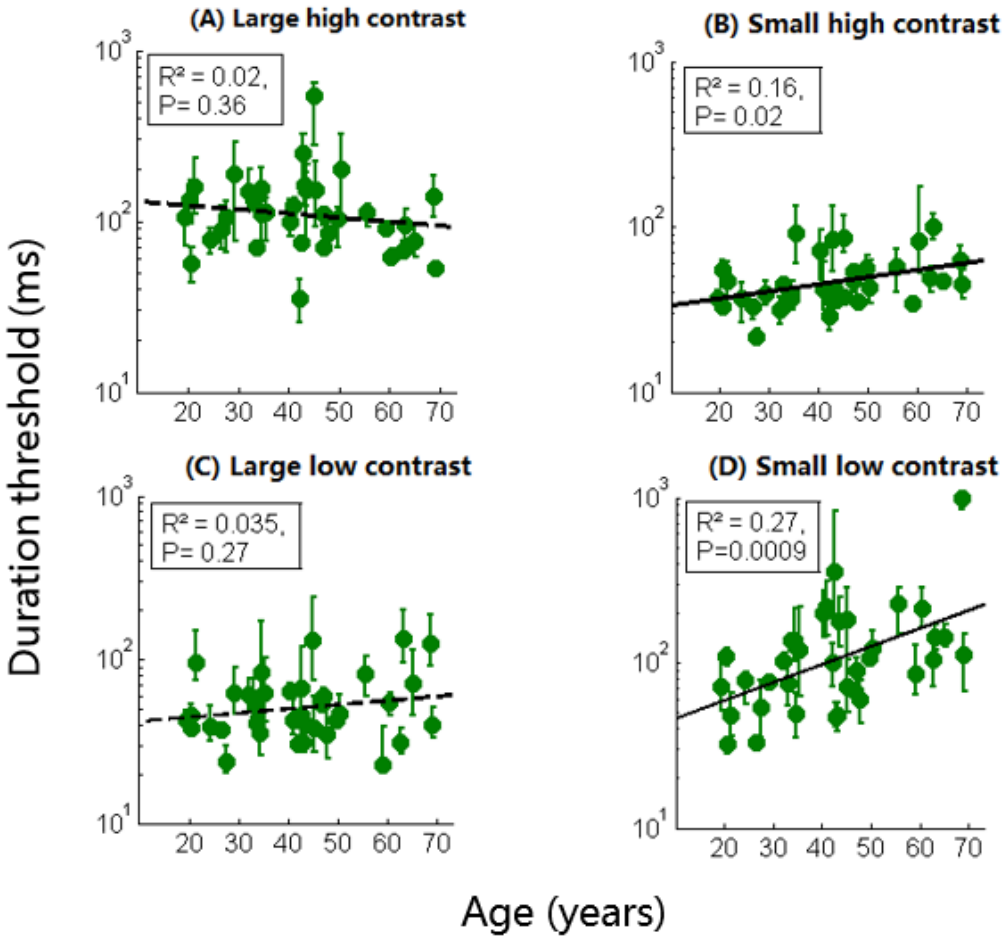


Figure 3.1. Plot showing duration thresholds as a function of age on log axes for 36 healthy participants for the motion discrimination task. A is large high contrast (92%), B small high contrast (92%), C large low contrast (2.8%), and D small low contrast (2.8%). Error bars show 95% confidence intervals. The black solid lines show significant regression with age, and dashed lines non-significant regression with age. R^2 and p values are shown in each panel.

3.2.2 Magnitude of motion suppression declines with age, while the magnitude of motion summation increases

Motion suppression and motion summation indices (Equation 2.2) were plotted as a function of age (Figure 3.2). Both motion indices showed a significant decrease with age (p=0.01 for both motion suppression and summation index). However, the effect of age on the magnitude of each index was opposite. Motion suppression indices were mainly positive in youth declining towards zero in age, while motion summation indices were near zero in youth declining towards more

negative numbers in age. This means that the magnitude of motion suppression decreases with age, while the magnitude of motion summation increases.

Motion suppression indices were mainly positive, and motion summation indices negative, meaning that while the magnitude of motion suppression index decreases with age, the magnitude of motion summation index increases with age, that is summation index was stronger in older participants. Moreover, as duration thresholds for large and small low contrast were very close (Figure 3.1), spatial summation was nearly absent in younger participants (Figure 3.2 B).

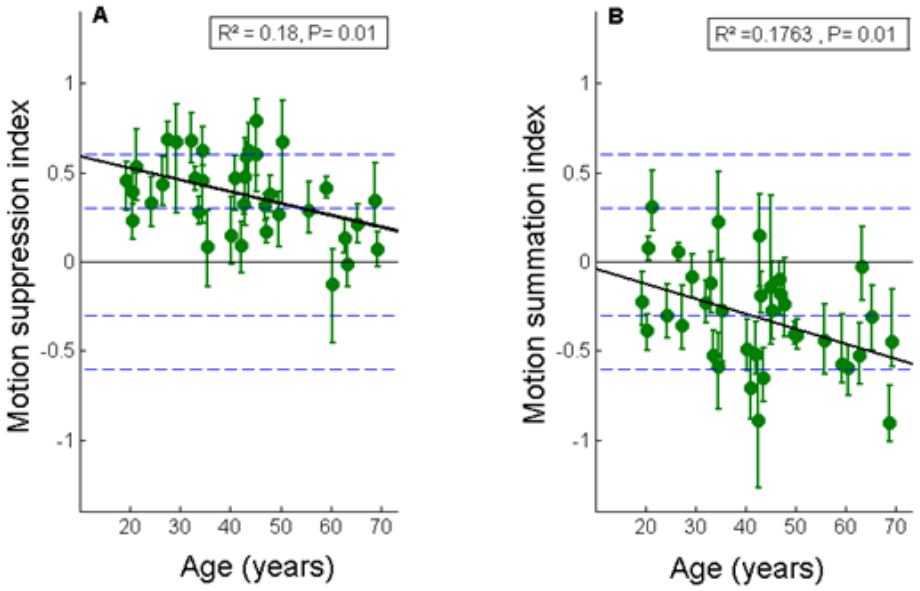


Figure 3.2. Motion-discrimination task: index is log ratio of large/small duration thresholds, shown for 36 subjects as a function of age. (A) Suppression index for high contrast stimuli; (B) summation index for low contrast stimuli. As before, error-bars show 95% confidence intervals, and the black line is the regression line. The solid horizontal line shows index=0, i.e. thresholds are the same for large vs small stimuli. The inner and outer dashed lines mark values of the index where thresholds differ by a factor of 2 and 4 respectively. The fitted regression lines are: (A) Index=-0.006*(Age in years)+ 0.65 and (B) Index =-0.0085*(Age in years) +0.04. R^2 and p values are marked in each panel.

Betts et al. (2005) showed similar results of decline in their population for a motion discrimination task, with a slope of 0.004 per year and average of around

0.02 at 23 years old and 0 at 68 years old. Motion suppression index was fractionally higher than what Betts et al found at around 0.5 at 25 years with a slope of 0.006 per year (Figure 3.2 A). Summation index also declines with age at a similar rate (0.008 per year; Figure 3.2 B). This decline is slightly sharper than that implied by the difference between the "younger" and "older" groups of Betts et al. (2005).

Motion suppression and motion summation indices both decrease with age, suggestive that they may be positively correlated. No such correlation was found, though, when the paired indices from individuals were plotted (Figure 3.3). The plot shows a positive slope, but the regression line between the two is non-significant ($p= 0.16$). Figure 3.3 also showed that most observers lay in the bottom right quadrant, which means that they show motion summation at low contrasts, and motion suppression at high contrasts. Nevertheless, even though the relationship between the two indices was not significant, participants with the highest motion suppression index showed lowest motion summation index (they tend to be younger). Also, those with the least suppression showed the highest magnitude of summation indices (and they are older).

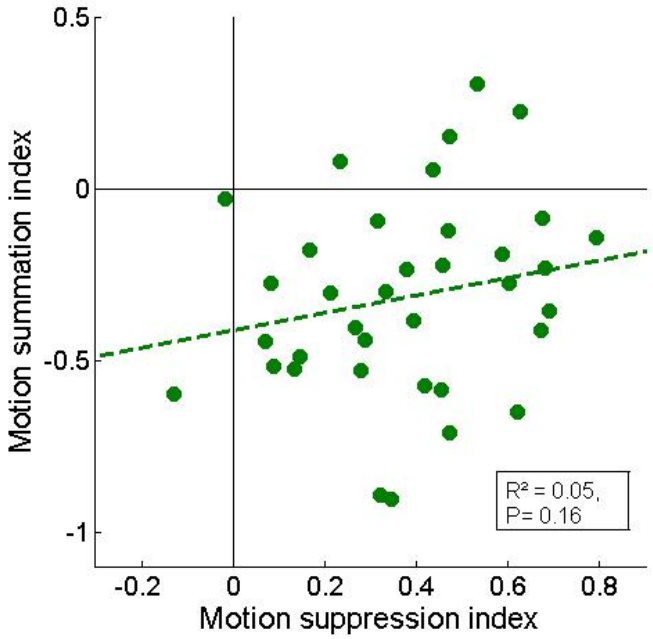


Figure 3.3. Scatter-plot of motion summation index against suppression index for 36 subjects. R^2 and p values for the Pearson correlation coefficient are marked in the box. The green line shows the regression line, fitted assuming that both variables are subject to the same amount of error (Draper and Smith, 1998). The slope of this regression also did not differ significantly from zero. The solid black lines show index = 0.

3.2.3 Significant correlation between motion discrimination task and age, but not for the contrast detection task

While Figure 3.2A shows a significant correlation between motion suppression index and age, there was no significant relationship between contrast suppression index and age. Figure 3.4 shows that contrast suppression index (Equation 2.3) had no correlation with age for 36 participants (R^2=0.003, p=0.75). The surround suppression index was 0.56 $\pm$ 0.2 (mean $\pm$ population SD). The fact that contrast suppression index is independent of age comes from a roughly equal increase in both parallel and orthogonal surround thresholds with age (Figure 3.5), which means the ratio of thresholds stays constant. Figure 3.5 shows that contrast thresholds increase with age in both (A) parallel and (B) orthogonal

conditions, however this increase was only significant for orthogonal surround (p=0.006).

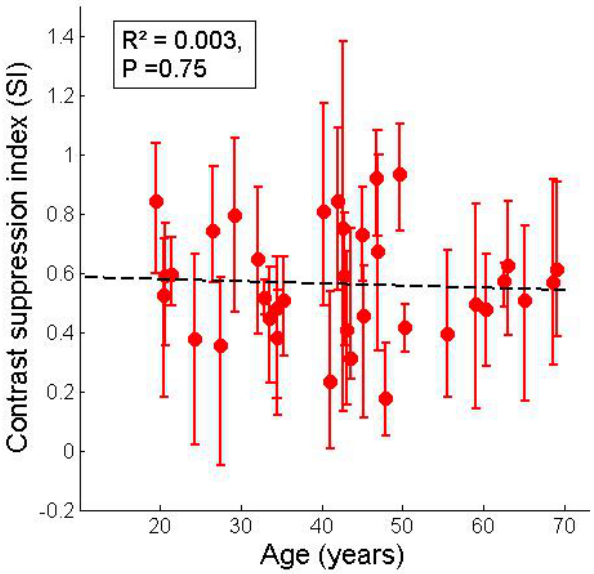


Figure 3.4. Contrast suppression index of the contrast detection task for 36 subjects as a function of age. Error-bars show 95% confidence intervals, and the black dashed line is the regression between contrast suppression index and age. There is no significant relationship between age and surround index (p=0.75).

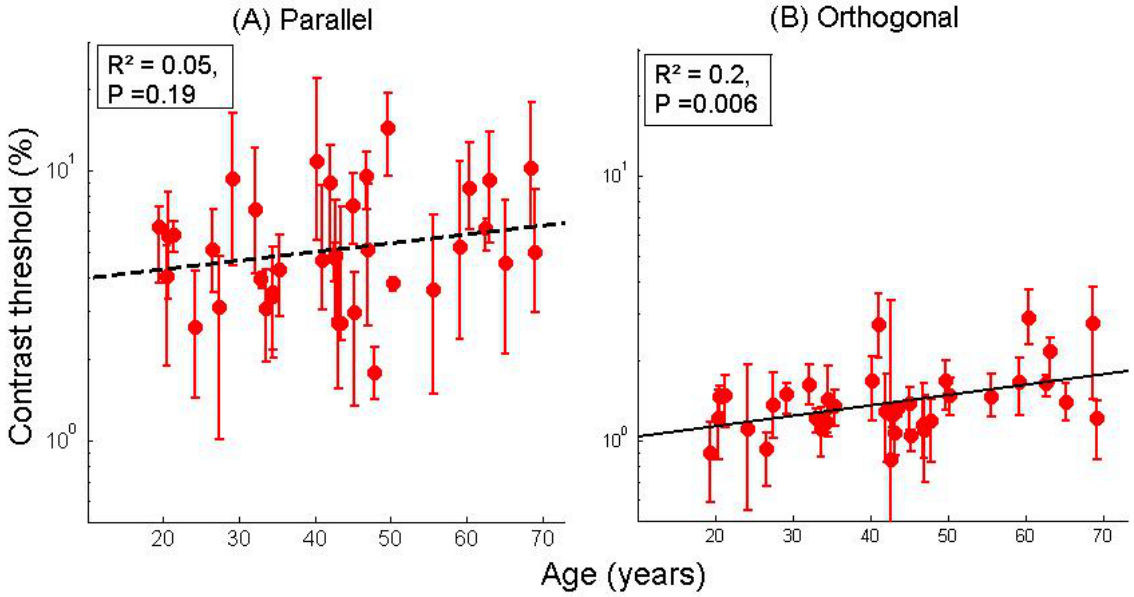


Figure 3.5. Contrast thresholds for the contrast detection task, plotted against age, when the background grating was (A) parallel or (B) orthogonal to the target. Error-bars show 95% confidence interval. Solid line is where the regression with age was significant, dashed line where it was non-significant. R^2 and P values are marked in each panel. The fitted regression lines are (A) $\log_{10}$ (threshold) =0.003*(Age in years) + 0.57; (B) $\log_{10}$ (threshold) =0.004*(Age in years) -0.02.

3.2.4 Motion suppression and contrast suppression indices are not correlated between individuals

I then asked if there was a relationship between motion suppression and contrast suppression indices. For each individual who participated in both tasks they were plotted all against each other. If both indices measured the same underlying quantity, points should be scattered around the line of equality. Figure 3.6 depicts this relationship for 36 participants with the black solid line representing the line of equality. The population means and standard deviations were relatively similar for both suppression indices, 0.40 (SD=0.22) for the motion discrimination task, and 0.56 (SD=0.19) for the contrast detection task, but critically, the two suppression indices were not correlated with one another. Green dashed line shows non-significant regression line (p=0.24).

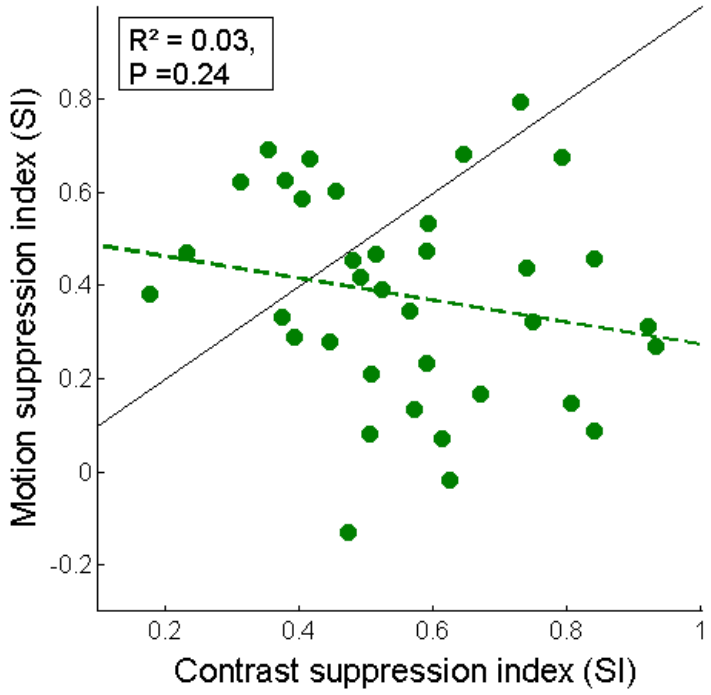


Figure 3.6. Scatter plot of surround suppression index of motion discrimination task compared to contrast detection task for 36 participants. The dashed line is the regression line (p=0.24) and the solid black line indicates the line of equality. There is no significant correlation between motion discrimination SI and contrast detection SI (correlation coefficient RHO= -0.1978, p=0.24).

3.2.5 No significant relationship between motion suppression and contrast suppression indices with orientation discrimination threshold between individuals

The important role of GABAergic inhibition is well documented in orientation selectivity (Allison and Bonds, 1994, Hubel and Wiesel, 1962, Blakemore and Tobin, 1972). Moreover, there is a strong link between orientation discrimination performance and GABA concentration (Edden et al., 2009a, Ferster et al., 1996, Ferster and Miller, 2000).

A study done by Edden et al. (2009a) showed that individual performance on a task of orientation is correlated with resting concentration of GABA in the primary visual cortex (V1). Concentration of GABA measured by magnetic resonance spectroscopy was significantly negatively correlated with orientation thresholds for obliquely oriented patterns. They showed for the first time that individual performance on a visual psychophysics task could be linked to GABA concentration in humans. We argued that if motion and contrast suppression indices are ways of assessing cortical inhibition, then it might be possible to compare them with an orientation task. Therefore, we used a similar test to that of Edden et al. (2009a) as a pilot study to further investigate the relationship between different psychophysical surround suppression tasks. Orientation discrimination threshold was used for seven healthy participants. Correlation analysis between motion suppression index and orientation discrimination threshold proved to be non-significant (Figure 3.7 A, a negative trend with $p=0.63$). Similar behaviour was observed for contrast suppression index and orientation threshold with a non-significant regression line (Figure 3.7 B, $p=0.55$). However, with only 7 subjects and lack of power it is not possible to rule out a correlation.

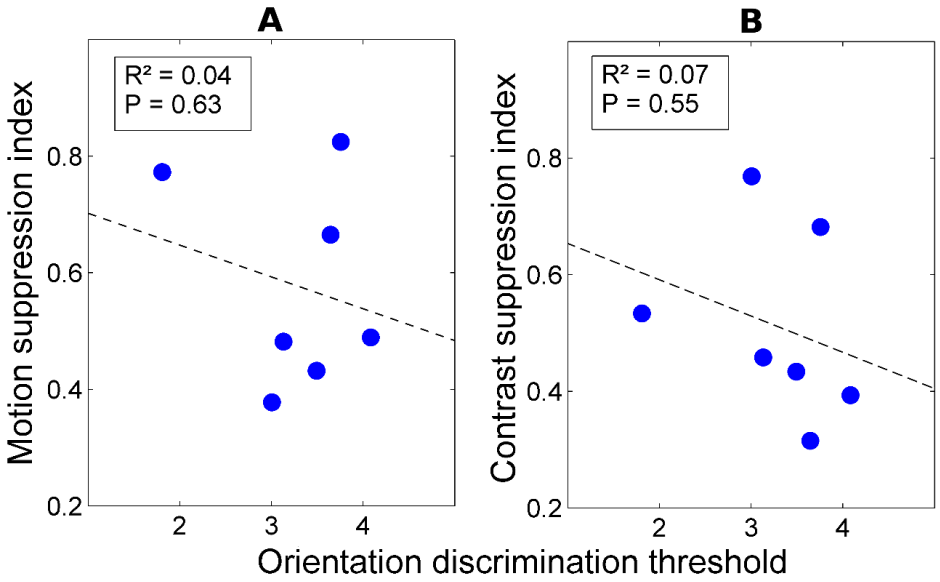


Figure 3.7. Scatter plot of motion suppression index (A) and contrast suppression index (B) against orientation discrimination threshold for 7 healthy participants. The dashed black line is the non-significant regression line, fitted assuming that both variables are subject to the same amount of error (A: p=0.63, B: p=0.55) (Draper and Smith, 1998).

3.2.6 Significant difference in suppression indices between female and male participants in the contrast detection task only

There are a number of studies suggesting the possibility of gender differences in the structure of V5/MT (Amunts et al., 2007). A study by Cohn et al. (1985) indicated that a strong stimulus to V5/MT produced larger amplitudes in young female participants compared to young males with differences weakening with increasing age (age range: 5-14 years old). Regional specific differences between men and women, and lower BOLD amplitudes in women were reported in a fMRI study (Kaufmann et al., 2001). A pattern reversal study showed that the P1 component of the visual-evoked potential was considerably shorter in female than male infants (Malcolm et al., 2002). Central field stimulation produced a larger right than left-hemispheric response in females, whereas males had only nonsignificant larger left hemisphere event-related potentials, suggesting a

greater right-hemispheric responsiveness to moving stimuli in females (Andreassi and Juszczak, 1982).

To assess the effect of gender on suppression indices, average of motion suppression index (Figure 3.8; green) and contrast suppression index (Figure 3.8; red) were plotted for female and male participants. The bar chart shows 26 female and 9 male mean suppression indices for motion discrimination task in green, and contrast detection task in red. Average age of female participants was 43 years old and 40 years old for male. The significant difference is only among men and women in contrast detection task ($p=0.02$). In order to find differences in means of multiple groups, one-way ANOVA test was applied. ANOVA only shows if there is any significant difference between groups. Then, post hoc comparison procedures should be conducted to find where the significant difference is. However this will not tell any information regarding the p values. In this case pair wise comparisons between means must be applied. On the other hand, this might increase the risk of Type 1 error, which is the probability of rejecting the null hypothesis by mistake. To address this issue, Bonferroni correction was used. The significant p value after Bonferroni correction is 0.02 (0.05/2). As a result, $p=0.02$ is survived after the Bonferroni correction and is in fact a significant difference.

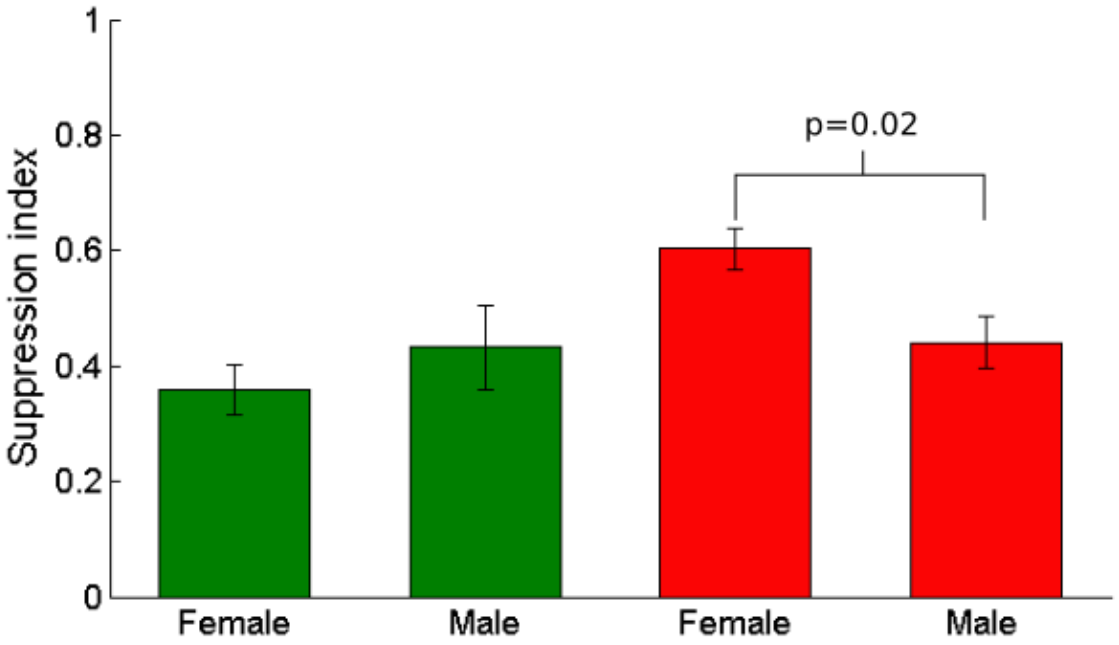


Figure 3.8. Bar chart of motion suppression indices is shown in green for male and female participants (26 female, 9 male), and in red for contrast suppression indices. There was no significant difference between female and male in motion suppression task (p=0.41). There was a significant difference among female and male in contrast detection task (p=0.02). Error bars are standard error of mean.

3.3 Discussion

Surround suppression is found in many visual cortical areas, for example in primary visual cortex V1 (Allman et al., 1985a, Sengpiel et al., 1998, Sengpiel et al., 1997), secondary visual cortex V2 (Shushruth et al., 2009), and V5/middle temporal (Allman et al., 1985a, Huang et al., 2007, Huang et al., 2008, Tsui and Pack, 2011). This has led to the assumption that surround suppression is a fundamental property of visual system, and consequently a vast number of studies have focused on measuring psychophysical properties of surround suppression. Recently, a growing number of studies have used changes in psychophysical surround suppression between healthy subjects and different patients groups to provide clinically useful information. For example, Tadin et al. (2006) used motion suppression index, and found patients with schizophrenia had lower suppression index compared to controls. They found patients had significantly higher thresholds for small stimulus compared to controls, but had similar thresholds for large stimulus, causing their suppression index to be lower. Given that GABA is the main neurotransmitter underlying cortical inhibitory mechanisms, and there is a good body of evidence on deficits of GABAergic system in schizophrenia in the literature, they speculated the possibility of the role of GABA deficits in the observed abnormality in surround suppression in schizophrenia (Wassef et al., 2003, Tadin et al., 2006). In fact, using Magnetic Resonance Spectroscopy (MRS), Yoon et al. (2010) showed lower concentration of GABA (10% lower) in visual cortex of patients with schizophrenia (Yoon et al., 2010). A number of studies in human subjects and animals showed that this may be a result of reduced transcription of the 67 kDa isoform of glutamic acid decarboxylase (GAD67) within parvalbumin-staining cortical neurons (PV) (Akbarian et al., 1995, Yoon et al., 2010, Hashimoto et al., 2008, Hashimoto et al., 2003, Chattopadhyaya et al., 2007, Asada et al., 1997). Yoon et al. (2009) and Serrano-Pedraza et al. (2014) showed altered contrast suppression in patients

with schizophrenia. A study on motion discrimination task in patients with major depressive disorder also reported lower suppression indices (Golomb et al., 2009), and suggested that this was reflecting a deficit in GABAergic inhibition in these patients. In another study by Edden et al. (2009a) the importance of GABAergic inhibition in orientation selectivity was demonstrated, and showed that interindividual performance on an orientation discrimination task is related to GABA concentration. Using magnetic resonance spectroscopy (MRS) they demonstrated that differences in performance were correlated with the resting GABA concentration within an individual`s primary visual cortex (V1). In other words, orientation discrimination threshold may be a way of assessing cortical inhibition. Thus, in all these papers the suppression indices have been considered as a way of measuring cortical inhibition. However, how these psychophysical measures correlate to each other and what exactly they measure is not yet clear.

In this chapter, I have demonstrated that individual variations in the two examined suppression indices were not correlated. In fact, if anything, they are negatively correlated (Figure 3.6, p=0.24). The population means and standard deviations were quite similar for both indices, at 0.4 (SD=0.22) for motion discrimination task, and 0.56 (SD=0.19) for the contrast detection task, but the suppression indices were not correlated (ρ=-0.20). Error bars in Figure 3.2A for motion suppression index and Figure 3.4 for contrast suppression index were fairly unreliable. Each index is the log ratio of two thresholds, which are both, individually, subject to experimental noise. Specifically, the contrast detection task in the condition of parallel (Figure 3.5) was according to the participants the hardest among all the tests, meaning that participants had a large number of mistakes and uncertainty in this task. This could potentially explain the large error-bars in the contrast thresholds when the background grating was parallel

to the target and consequently in the contrast suppression index (Figure 3.4). How much the measurement error reduces the observed correlation depends on the size of the measurement error relative to the variability present in the population. In Read et al. (2015), in a similar population to here, we demonstrated that the true correlation considering the presence of the measurement noise (error) could only be as high as ρ=-0.27. Thus, it would be hard to consider them to be positively correlated. The fact that these two indices have different nature is further verified by showing their different relationship to age; Motion suppression index decreased with age, as does motion summation index (Figure 3.2), however the contrast suppression index showed no change with age (Figure 3.4). Conversely, Karas and McKendrick (2011) showed that contrast suppression increases with age with supra-threshold contrasts (Karas and McKendrick, 2011, Karas and McKendrick, 2009, Karas and McKendrick, 2012, Karas and McKendrick, 2015). These results suggest that the two suppression indices mirror different features of cortical functioning. Surround suppression index is in fact a division of two durations and is important to consider it as a relative measurement that depends on two measurements, a control condition (without surround) and a suppressive condition (with surround). It is not possible to know if for a particular subject suppression is strong or weak with only considering one absolute measurement in one condition. The justification to use duration thresholds is based on the assumption that if the neural response to a stimulus is weak and/or noisy, then a longer stimulus exposure is necessary for a correct perception (Tadin et al., 2006). That is a process of accumulation of sensory evidence over time is required to judge the moving direction of an object (Tadin et al., 2006, Gold and Shadlen, 2000, Roitman and Shadlen, 2002). Hence, a longer duration threshold (longer required exposure duration) could be evidence of noisy or attenuated neuronal responses.

The contrast suppression index shows selectivity for stimulus orientation, suggesting an early visual cortical locus (Yoon et al., 2010). Intracellular recordings of V1 neurons showed that a surround stimulus triggered an increase in inhibitory conductance, with a reduction in excitatory and inhibitory conductance, in which all showed orientation selective manner (Ozeki et al., 2009). In a study by Zenger-Landolt and Heeger (2003) fMRI responses as a function of contrast and psychophysical contrast thresholds were quantitatively compared, and they found that psychophysics explain 96.5% of the variance in the measured V1 responses, suggesting V1 to be a likely site for mediating surround masking. Spatial (Angelucci et al., 2002, Cavanaugh et al., 2002, Serrano-Pedraza et al., 2012) and temporal (Bair et al., 2003) properties of contrast surround suppression agrees with the properties of primary visual cortex V1 neurons. This antagonism is believed to be implemented by feedback projections from extrastriate cortex, mediated by inhibitory projections from nearby interneurons (Alitto and Dan, 2010, Angelucci and Bressloff, 2006, Yazdani et al., 2015). . In contrast, impaired visual performance in motion discrimination task has been speculated to be the perceptual correlate of antagonistic centre surround mechanisms (Westheimer, 1967, Tadin et al., 2003). Moreover, centre surround motion neurons are found in cortical areas V5/MT, primary visual cortex V1 (Jones et al., 2001), and medial superior temporal MST (Eifuku and Wurtz, 1998). From these areas, the critical size where the strong surround suppression starts is only similar to that of a V5/MT centre surround neuron (Tadin et al., 2003). Tadin et al. (2011) further showed that disruption of V5/MT by offline 1 Hz transcranial magnetic stimulation (TMS) improved motion discrimination of large moving stimuli by reducing the strength of surround suppression. Therefore, the motion suppression index is believed to reflect the receptive field properties of centre surround neurons in V5/MT (Tadin et al., 2003, Betts et al., 2012, Churan et al., 2008).

I also presented data investigating the relationship of motion and contrast suppression indices to orientation discrimination threshold (3.2.5). A human study done by Edden et al. (2009a) presented a link between animal neurophysiology and human behavioural studies, in which they showed that variability of threshold on an orientation detection task was significantly negatively correlated with resting GABA concentration in an individual`s cortex for obliquely orientated stimuli ($p<0.015$). Data in Figure 3.7 shows that orientation discrimination thresholds of seven healthy participants were not correlated with motion and contrast suppression indices (motion discrimination task: $p=0.63$, contrast detection task: $p=0.55$). However, with small numbers of participants, and the consequent lack of power, it is not possible to rule out a correlation. Another possible explanation might be that orientation discrimination thresholds are probably set in a different cortical area from the motion and contrast thresholds. Neuronal orientation preference might be partly due to feedback signals from higher level areas (V4 or V3)) (Liang et al., 2007). Therefore, if motion and contrast discrimination thresholds are measuring GABA inhibition within area V5/MT and V1, then it might perhaps explain the lack of significant relationship between them and orientation threshold.

A possible explanation for lack of correlation between motion and contrast indices might be that they indeed measure cortical inhibition in V5/MT and V1 respectively, but that inhibition in these different areas are independently modulated. However, it is not clear why contrast suppression index was not correlated with age. If contrast suppression index provides psychophysical estimates of the strength of GABAergic inhibition, then it should have shown a relationship with age. Several studies have suggested that the effective strength of GABAergic inhibition reduces with age, but this has been shown to affect both

V1 (Fu et al., 2013, Hua et al., 2008, Yu et al., 2006, Leventhal et al., 2003, Pinto et al., 2010) and MT (Liang et al., 2010).

Another possible reason might be that one or both of these indices does not provide psychophysical measure of cortical inhibition. Churan et al. (2008) showed that many visual cortical neurons do not show surround suppression, and only at brief stimuli (<40ms) MT centre surround neurons got activated. However, other studies have shown centre surround inhibition in long duration stimuli (Tadin et al., 2009, Aaen-Stockdale et al., 2009). Another study with a different theory claimed that psychophysical surround suppression may not be a perceptual correlate of surround-suppressed neurons in V5/MT, but it is due to the differences in contrast sensitivity at different sizes (Aaen-Stockdale et al., 2009). Using a different task, they showed that the effect of size vanishes when the contrast of different size stimuli was normalised relative to their contrast thresholds. To reject this justification, Glasser and Tadin (2010) used duration threshold measurements, and showed that strong spatial suppression was present even when the contrast of the stimuli were normalized relative to their contrast threshold. Thus, motion discrimination task does in fact reflect both surround suppression and spatial summation.

Another theory that might explain the independency of contrast and motion suppression indices is that there are a lot of studies arguing that there are physiologically distinct forms of surround suppression even within V1. For instance, activation of orientation tuned surround suppression in the lateral geniculate nucleus (LGN) might lead to reduced excitation in V1 (Ozeki et al., 2004), lateral connections within V1 were believed to form surround suppression (Gilbert and Wiesel, 1983), or more recently feedback connections from higher cortical areas (Webb et al., 2005, Angelucci and Bressloff, 2006, Ichida et al., 2007, Tailby et al., 2007, Bair et al., 2003). Therefore, the term “surround

suppression" that is used in different psychophysical studies might cover different neuronal mechanisms.

In addition, when comparing the suppression indices in males and female I observed a significant difference between male and female participants (with no significant difference in age) in the contrast detection task (Figure 3.8). The observed gender difference is unexpected, but hard to say if it is real. Our sample contained only 9 males as compared to 26 females; the difference is not highly significant ($p=0.02$) and this was not a planned comparison. This might be worth investigating in a future study.

Next chapter will show results of visual psychophysics in patients with epilepsy and the differences between controls and patients with different frequency of seizures.

Chapter 4 Relationship of seizure susceptibility to performance in psychophysics tests

4.1 Introduction

Surround suppression can be observed in many different areas, such as central nervous, motor (Beck and Hallett, 2011) and sensory systems (retina, somatosensory, vision). In visual neuroscience, surround suppression refers to reduction of a neuron's response to a stimuli situated outside of its classic receptive field (Benevento et al., 1972, Maffei and Fiorentini, 1976), and is believed to be mediated by GABAergic inhibitory connections (Alitto and Dan, 2010, Angelucci and Bressloff, 2006, Gieselmann and Thiele, 2008, Nurminen and Angelucci, 2014). Recently, there have been a number of studies investigating surround suppression in different patient groups using visual psychophysics. For example, surround inhibition is believed to be compromised in patients with schizophrenia (Lewis et al., 2005, del Pino et al., 2013), which leads to various cognitive impairments (Yoon et al., 2010). Using a motion discrimination task Tadin et al. (2006) showed that patients with schizophrenia had significantly weaker surround suppression compared to healthy controls, and those with severe symptoms had the lowest surround suppression index.

Interestingly, there is a high prevalence of psychotic episodes in patients with epilepsy (Sachdev, 1998, Slater et al., 1963). A study done by Gutierrez-Galve et al. (2012) showed that reduction in cortical thickness in the inferior frontal gyrus is implicated in psychosis and specifically temporal lobe epilepsy. Some studies suggested that patients with long duration of epilepsy were more susceptible to develop psychosis (Kanemoto et al., 2012). Patients with epilepsy were shown to have nearly 2.5 times the risk of developing schizophrenia in comparison with general population (Qin et al., 2005). There is also, a bidirectional link between

patients with schizophrenia and epilepsy (Chang et al., 2011), meaning that patients with schizophrenia are around 6 times more likely to have seizures.

Therefore, we speculated that visual psychophysics could potentially offer a non-invasive way of assessing the integrity of suppressive centre-surround mechanisms and disease state in epilepsy.

In this chapter, I will show the results of a group of 54 patients with epilepsy on the motion discrimination and the contrast detection tasks to compare them with 146 control participants, and to investigate if there is any significant difference between patients and healthy participants and whether this is related to patients' seizure frequency. We therefore compared surround suppression indices in patients with frequent seizures versus infrequent seizures, the prediction being that if seizures were generated due to the reduction in steady state inhibition, then psychophysical evidence of this would be expected to be observed as a lower surround suppression index.

4.1.1 A grading system to define frequent and infrequent seizures (Grading A and B)

There have been many efforts (Cramer and French, 2001) to find the best assessment of seizure severity in the past. The optimal method would be one that is easy to administer by patients and physicians, is precise and sensitive to changes after a modification in medication and does not intrude too much on the patient's time and effort. The most important criterion is that the method is relevant to the individual and reflects on their quality of life: some people are happy with 3 seizures a month, however for others, 3 seizures/month is a disaster. After all epilepsy is a set of conditions that not only affects patients' health, but also their families' day to day lives.

One of our goals was to grade seizure frequency, but there is no universally accepted scale for this. Several rating scales are available that assess severity of epilepsy based on several measures including quality of life, and an assessment of seizure frequency. Examples of these scales are VA scale (Cramer et al., 1983), Chalfont seizure severity scale (Duncan and Sander, 1991), the national hospital seizure severity scale (O'Donoghue et al., 1996), Liverpool scale (Baker et al., 1998) and recently the Global Assessment of Severity of Epilepsy (GASE) Scale in children (Chan, 2014). Given that there was no single consistent means of assessing seizure frequency between these scales, we came up with our own, based on the seizure frequency.

Patients were divided into two groups: patients with frequent seizures and patients with infrequent seizures. Due to the lack of precise information regarding seizure frequency, a new system was administered in this study. Table 4.1 depicts this method, which was used to systematically sort these reported numbers into five different categories. This table ranges from category 1 (least severe) to 5 (most severe), where category 1 represents patients with only one reported seizure or multiple seizures occurring one or more years apart during the last three years and category 5 which represents patients with one or more seizures per day.

Dividing patients into these five categories proved to be challenging because many patients fell in the border line of two or more categories, or the reported frequency of seizures was not always accurate. We therefore felt it was inappropriate to perform sub-group analysis on what were ill-defined groups, and instead amalgamated these into two groupings of “frequent” versus “infrequent” seizures. The definition of frequent in this setting is of course arbitrary, and we therefore examined two different cut-offs for this definition,

“grading A” and “grading B”. Grading B was defined to examine the robustness of observed results in Grading A.

Based on Table 4.1 in grading A, a patient with one or more than one seizure per week, and in grading B a patient with one or more than one seizure per month were considered as a patient with frequent seizures. Based on this, grading A consisted of 20 patients with frequent and 34 patients with infrequent seizures, and, grading B comprised of 35 patients with frequent seizures and 19 patients with infrequent seizures. Other groups have defined frequent and infrequent seizures based on scores giving to patients based on counting seizures, using cardinal scales (few, many, fewer or more seizures) or patients’ self-reports of their seizure frequency. A review of all these methods can be found in Cramer and French (2001). But defining frequency based on “grading A” and “grading B” made it possible to assess how robust our results were, given the inherent unreliability of the reported number of seizures.

There is a strong link between sensory discrimination and intelligence quotients (IQ) (Melnick et al., 2013, Tadin, 2015). Melnick et al. (2013) showed that participants with higher IQ were better at discriminating moving of the small stimuli, however needed more time to perceive larger stimuli. Therefore, cognitive function was measured to account for the possibility of IQ being a potential confound for the measured surround suppression. Cognitive function among patients with epilepsy is generally described by deterioration of memory function (Motamedi and Meador, 2003). Therefore, patients were interviewed and assessed for cognitive impairment. Addenbrooke’s Cognitive Examination-Revised (ACE-R) is a useful method for identifying mild cognitive impairment and dementia and measuring six cognitive domains including: orientation, attention, memory, verbal fluency, language, and visuospatial ability (Mioshi et al., 2006). All patients were above the cut-off threshold (cut off score 75). Although test of

ACE-R is superior to most of available tools for cognitive examination, it has some downsides. For example, there are other patterns reflecting on cognitive dysfunction in patients with epilepsy, such as reduced speed processing (Dow et al., 2004, Arzimanoglou et al., 2005), attention and executive dysfunction (Stretton and Thompson, 2012). One of the problems with ACE-R is that only five points of it is allocated to attention and it is largely influenced by level of education of patients (Komadina et al., 2011).

Table 4.1. Description of the scale used to determine seizure frequency. Grading A consisted of infrequent (frequency 1, 2, 3) and frequent (frequency 4, 5). Grading B consisted of infrequent (1, 2) and frequent (3, 4, 5).

Seizure frequency	Description	Grading A	Grading B
1	More than a year was between each seizure	Infrequent	Infrequent
2	More than or equal to 1 per year, but less than 1 per month		
3	More than or equal to 1 per month, but less than 1 per week		Frequent
4	More than or equal to 1 per week, but less than 1 per day	Frequent	
5	More than or equal to 1 per day		

4.1.2 Data analysis

Parametric tests such as regression analysis and ANOVA assume that data fit the normal distribution. Therefore, data must be checked for normality before any statistical analysis. One method of assessing normality is to perform the probability plot or Quantile-Quantile (Q-Q) plot in SPSS. This test is a powerful

analysis compared to histograms and is a non-parametric approach to check data distribution. If data is normally distributed, the points shown on Q-Q plot lie on a straight diagonal line.

As age was shown to be a confounding factor, an analysis of regression was followed to check if age confound was the reason that the distributions were not normal or Gaussian. First a line of best fit was plotted for all three groups. Residuals are the difference between the observed value of each data set and predicted value by the line of best fit. In order to compress data into a single number without the effect of age, residuals were plotted from the line of best fit and checked if they are around zero.

In order to compare the groups with each other, Kruskal-Wallis which is a non-parametric test, was used. Kruskal-Wallis is the equivalent to ANOVA to compare three or more groups together.

As an alternative test, Kolmogorov-Smirnov (KS), another non parametric test, was used to compare cumulative probabilities of different groups to find their differences. In order to perform the KS-test, cumulative distributions of different groups were plotted and the statistic D, which is the maximum difference between cumulative distributions, was calculated.

The null hypothesis is that samples are drawn from the same distribution, and can be rejected at level α if:

$$D_{n1,n2} > c(\alpha) * \sqrt{\frac{n_1+n_2}{n_1*n_2}}$$

Equation 4.1. The Kolmogorov-Smirnov test.

And the value of c(α) can be derived from Table 4.2.

Table 4.2. The value of c(α) is given in the above table for each level of α.

α	0.10	0.05	0.025	0.01	0.005	0.001
c(α)	1.22	1.36	1.48	1.63	1.73	1.95

4.2 Results

4.2.1 Analysis of the motion discrimination task

Duration thresholds were measured and plotted against age for 146 healthy controls (Figure 4.1) and 54 patients with epilepsy (Figure 4.2). The top panels in both figures show duration thresholds of high contrast (A-B), and the bottom duration thresholds of low contrast (C-D).

In Figure 4.1, as for data presented in chapter 3, duration thresholds of control participants were found to be longer in large high contrast stimuli than for small high contrast stimuli. Also, comparable results were observed for regression lines, where duration thresholds increased with age in small high contrast ($p<0.001$) and small low contrast ($p<0.001$).

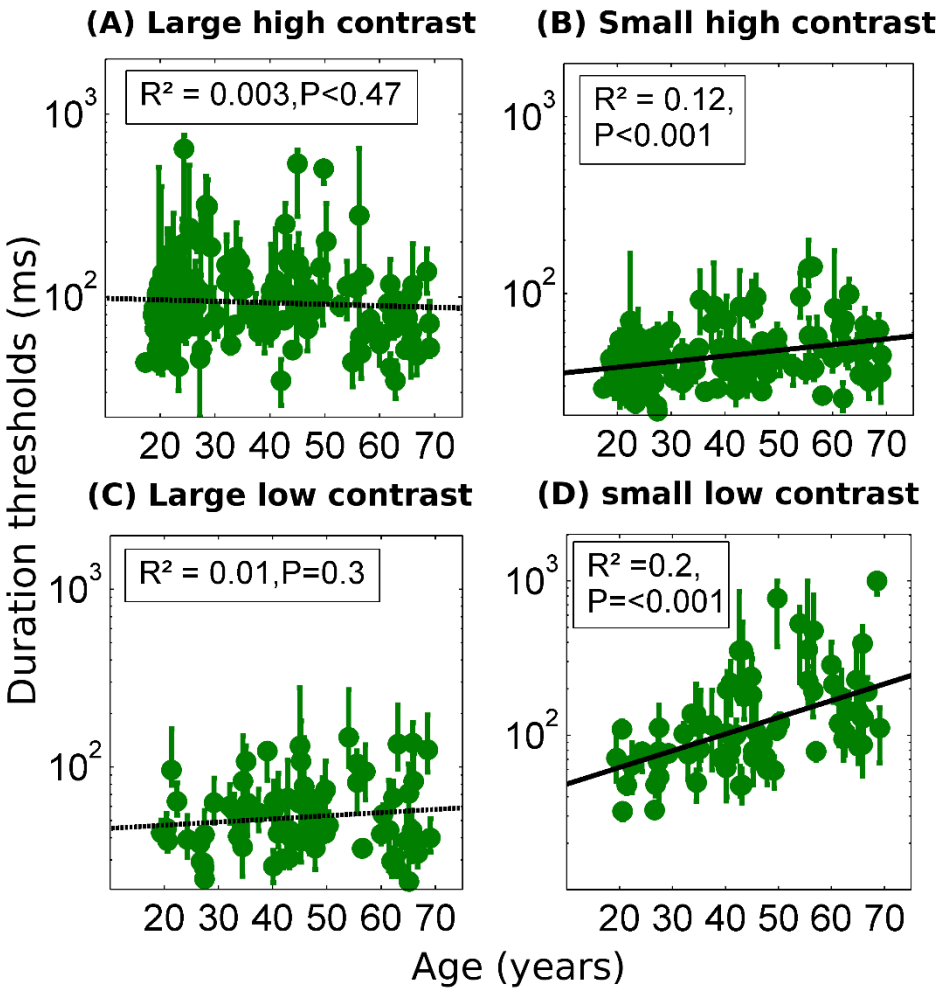


Figure 4.1. Duration thresholds of 146 healthy participants as a function of age on log axes for the motion discrimination task. Four stimulus conditions are shown: (A) Large high contrast (92%), (B) Small high contrast (92%), (C) Large low contrast (2.8%), and (D) Small low contrast (2.8%). Error bars show 95% confidence intervals. Lines show regression with age; solid lines are those where the regression with age was significant, dashed lines where it was non-significant. R^2 and p values are marked in each panel.

Figure 4.2 shows duration thresholds of 54 patients with epilepsy as a function of age. Similar to controls, high contrast duration thresholds were longer in large stimuli compared to small high contrast. And, in low contrast duration thresholds were relatively shorter in large than small stimuli. For the purpose of comparison, Figure 4.1 and Figure 4.2 are superimposed in Figure 4.3.

Similar trends in regression lines were observed between patients and controls duration thresholds in all conditions except in large high contrast. A steep significant regression line in large high contrast was observed for patients, whereas controls showed a non-significant steady regression with age.

Another difference is in small high contrast where on the contrary to controls regression line did not reach significance (Figure 4.3 B, p=0.26).

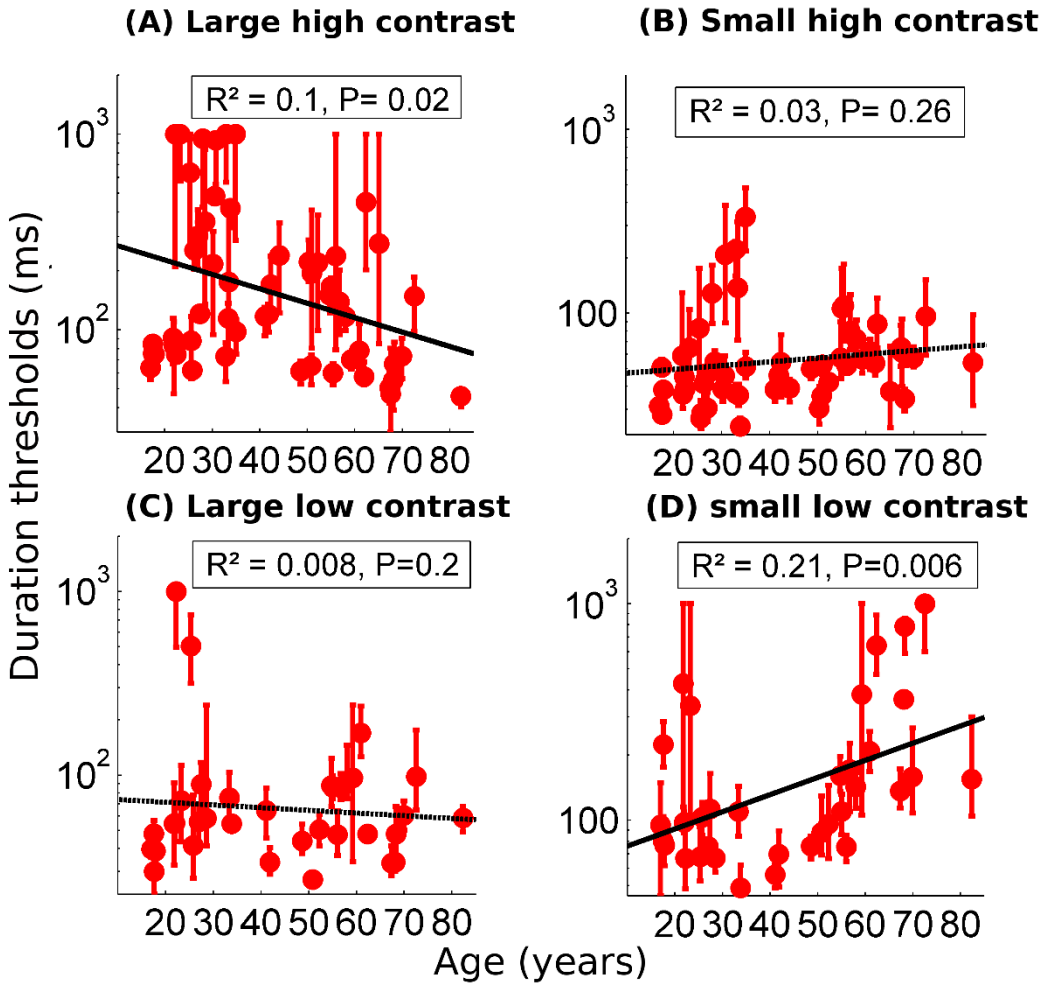


Figure 4.2. Duration thresholds of 54 patients plotted as a function of age on semi-log axes for the motion discrimination task. Four stimulus conditions are shown: (A) Large high contrast (92%), (B) Small high contrast (92%), (C) Large low contrast (2.8%), and (D) Small low contrast (2.8%). Error bars show 95% confidence intervals. Lines show regression with age; solid lines are those where the regression with age was significant, dashed lines where it was non-significant. R^2 and p values are marked in each panel.

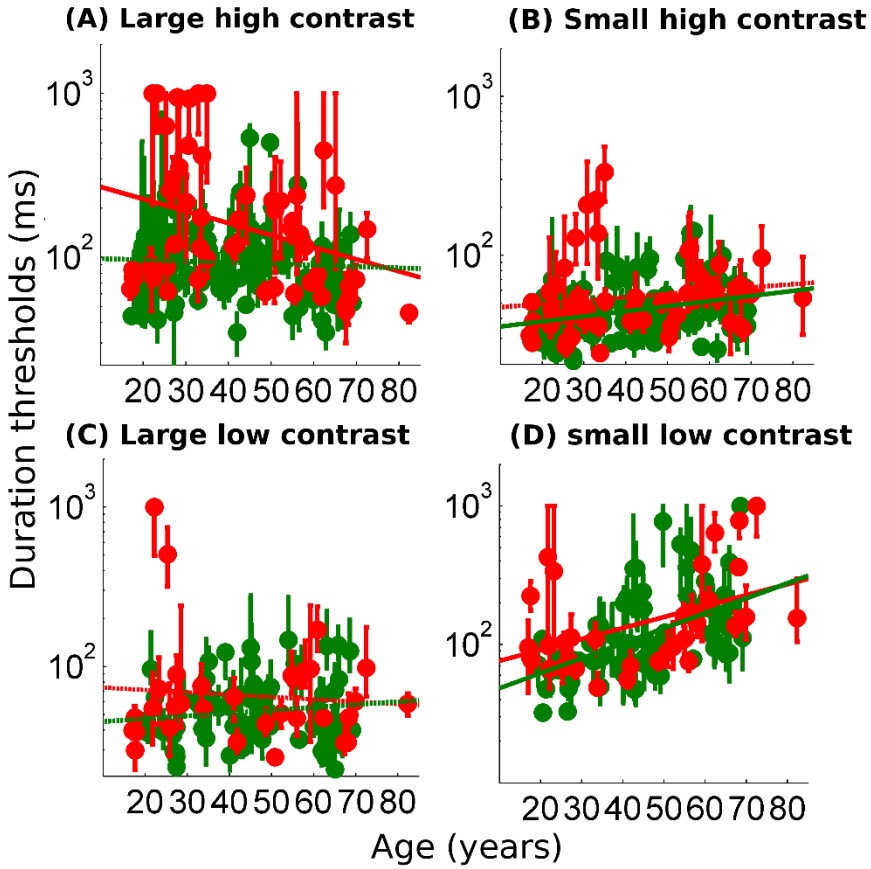


Figure 4.3. Overlaid duration thresholds of 146 healthy controls (in green) and 54 patients with epilepsy (in red) for the motion discrimination task.

An interesting difference between patients and healthy controls was that a number of patients showed an exceedingly long duration thresholds for the large high contrast. Figure 4.3 A shows a few patients had very high duration thresholds (around 1000ms). These high durations are not exactly 1000ms, but rather that the staircase method could not estimate a threshold because the subject made repeated false judgements (mistakes) of the direction of grating movement. Also, there were a couple of patients with similar long duration thresholds in large low contrast (Figure 4.3 C). These long durations were not reported in other similar studies (Betts et al., 2009, Tadin et al., 2006, Tadin et al., 2003). There was no significant difference in these patients' seizure frequencies to others.

Figure 4.4 and Figure 4.5 further explore these differences.

Figure 4.4 shows frequency of duration thresholds for both patients and healthy participants for large high (top panel) and small high (bottom panel) stimuli. It is noticeable that there are 6 patients with duration thresholds of over 900ms in large high contrast (Figure 4.4-Top panel around 11% of total number of patients). However, the maximum duration thresholds of controls were between 600 - 700ms (around 2% of total number of controls). Figure 4.5 is normalised cumulative frequency plots of duration thresholds in controls and patients which show a deviation of the two samples' distributions at the high tail end in the large high contrast Figure 4.5, top figure). Kolmogorov-Smirnov test (K-S) showed that the two distributions are significantly different in the large high contrast at p=0.005.

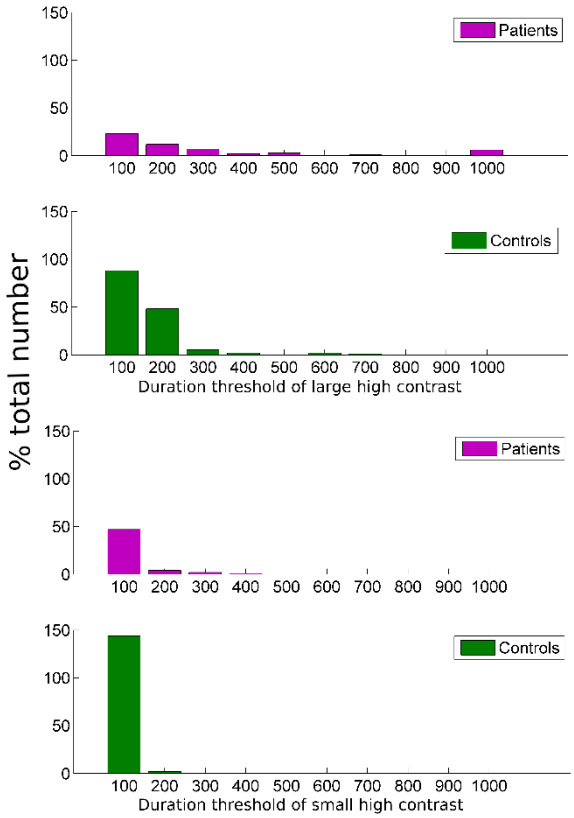


Figure 4.4. Frequency histogram of duration thresholds of 146 healthy controls and 54 patients with epilepsy were plotted in large high (top panel) and small high (bottom panel) contrasts.

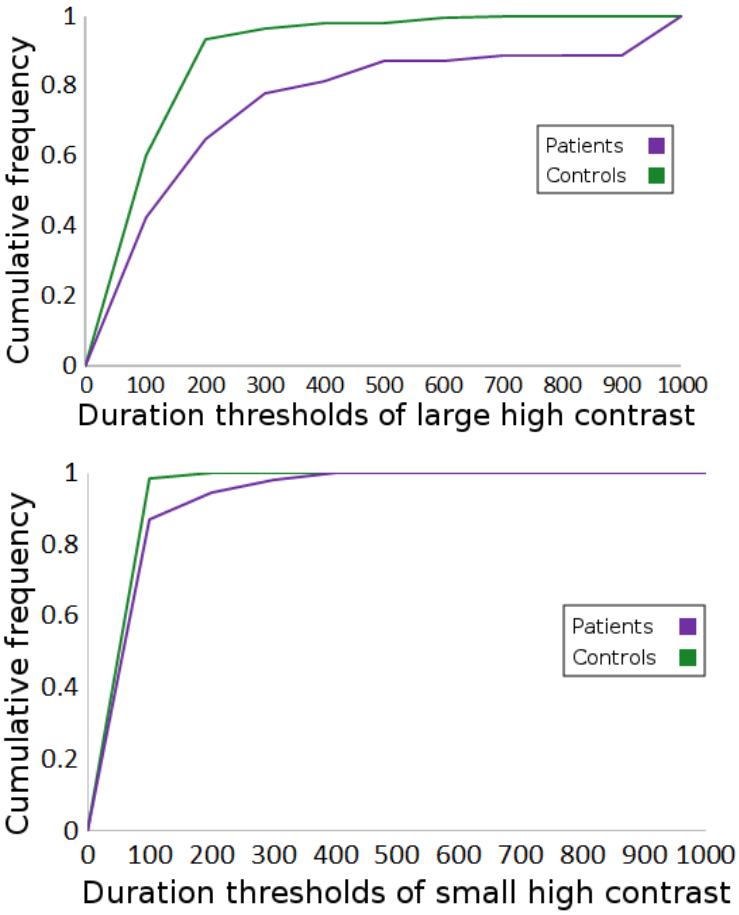


Figure 4.5. Normalised cumulative frequency plots of duration thresholds for large (top) and small (bottom) high contrast for 54 patients (in purple) and 146 controls (in green). The cumulative relative frequency of patients and controls are significantly different in large high contrast at p=0.005.

Motion suppression index (Equation 2.2) of 146 controls and 54 patients with epilepsy were plotted against age in Figure 4.6. There was a significant decrease in motion suppression in both groups with increase of age (in both patients and controls: $p<0.001$). Magnitude of motion suppression decreased with age in both controls and patients.

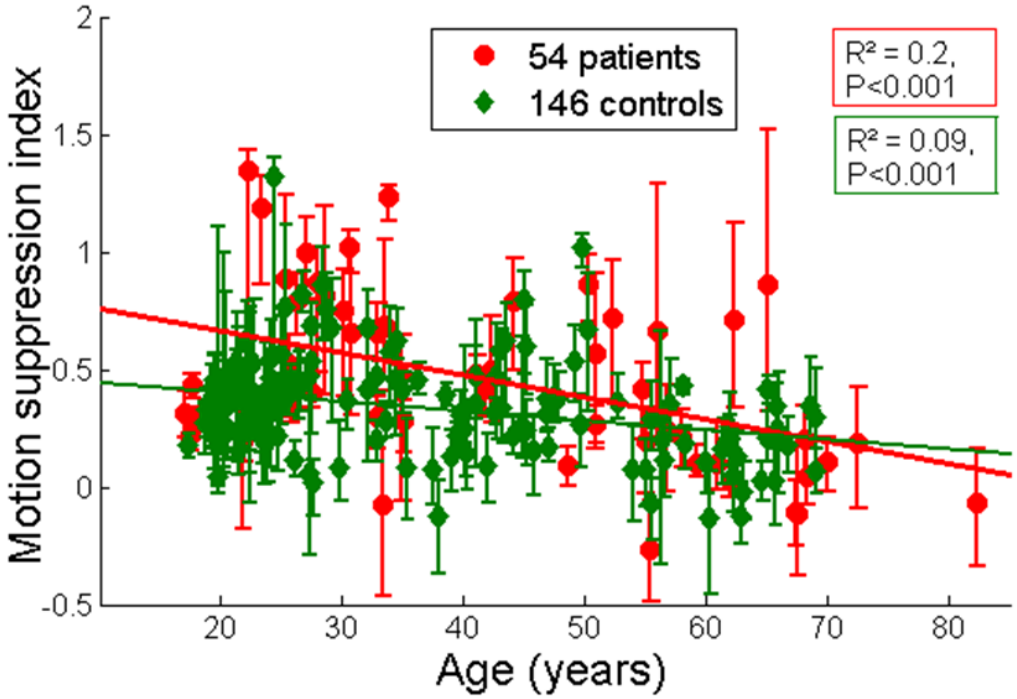


Figure 4.6. Motion suppression index plotted as a function of age. Motion suppression index, the log ratio of large/small duration thresholds, is shown for 54 patients in red and 146 healthy participants in green. Error-bars show 95% confidence intervals, and solid lines are significant regression lines (Patients: Index= -0.0094*(Age in years) + 0.852; Controls: Index= -0.0040 *(Age in years) + 0.4833.

4.2.2 Analysis of the contrast detection task

Impaired contrast detection could be a confounding factor in the motion discrimination task. Moreover, there have been some studies using contrast detection tasks to measure inhibition in schizophrenia (Serrano-Pedraza et al., 2014, Ekstrom et al., 2015, Slaghuis, Keri et al., 2002). The contrast detection task is a grating situated in the visual periphery which becomes less visible if is surrounded by a grating with the same spatial frequency and orientation (Petrov et al., 2005, Lev and Polat, 2011, Snowden and Hammett, 1998a, Xing and Heeger, 2000). We hypothesised that this experiment as well as the motion discrimination task might show possible cortical alterations including reduced

concentration of GABA which affects surround suppression in patients with epilepsy (Serrano-Pedraza et al., 2014). To compare performance of patients and healthy participants in the contrast detection task, contrast thresholds of 43 controls and 34 patients with epilepsy were plotted against age in Figure 4.7. There was a significant relationship between contrast thresholds and age in both parallel and orthogonal in patients (Figure 4.7C, p=0.002 and in D, p= 0.01). However, in controls significant correlation with age was only observed in orthogonal condition (Figure 4.7B, p=0.002). Both patients and control participants showed more variability and longer thresholds in parallel condition (Figure 4.7 A and C), which might be because it was a harder task relative to orthogonal (Serrano-Pedraza et al., 2014, Petrov et al., 2005, Lev and Polat, 2011, Ejima and Takahashi, 1985, Snowden and Hammett, 1998a). Figure 4.8 shows superimposed contrast thresholds of controls and patients.

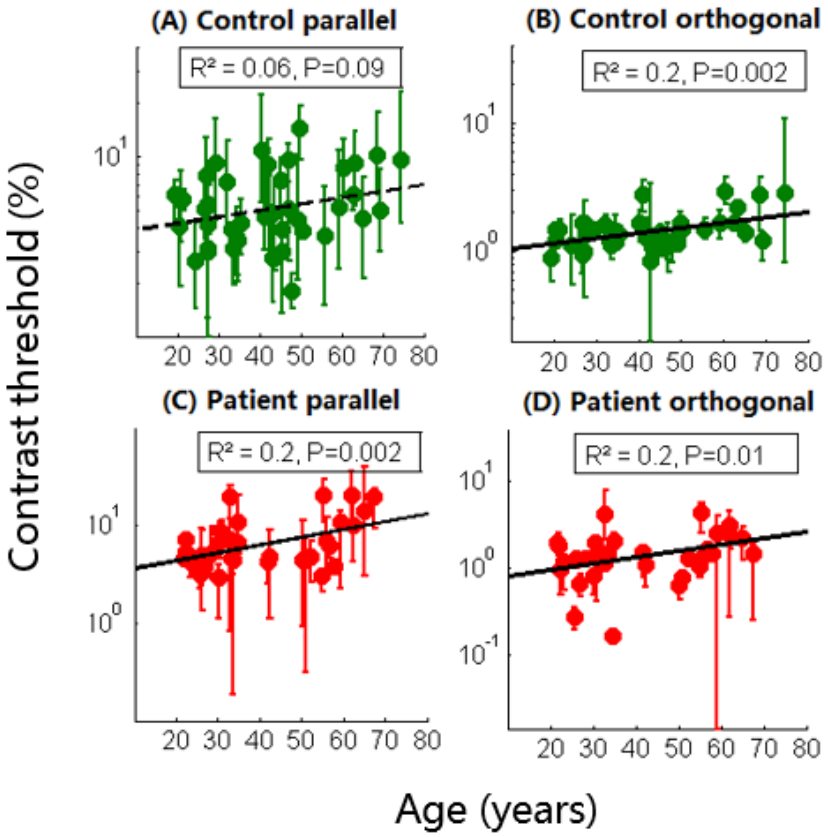


Figure 4.7. Contrast thresholds for contrast detection task plotted against age for 43 controls and 34 patients with epilepsy, when the background grating was parallel (A, C) or orthogonal (B, D) to the target. Error-bars show 95% confidence interval. The solid line is where the regression with age was significant, the dashed line where it was non-significant. R^2 and P values are marked in each panel.

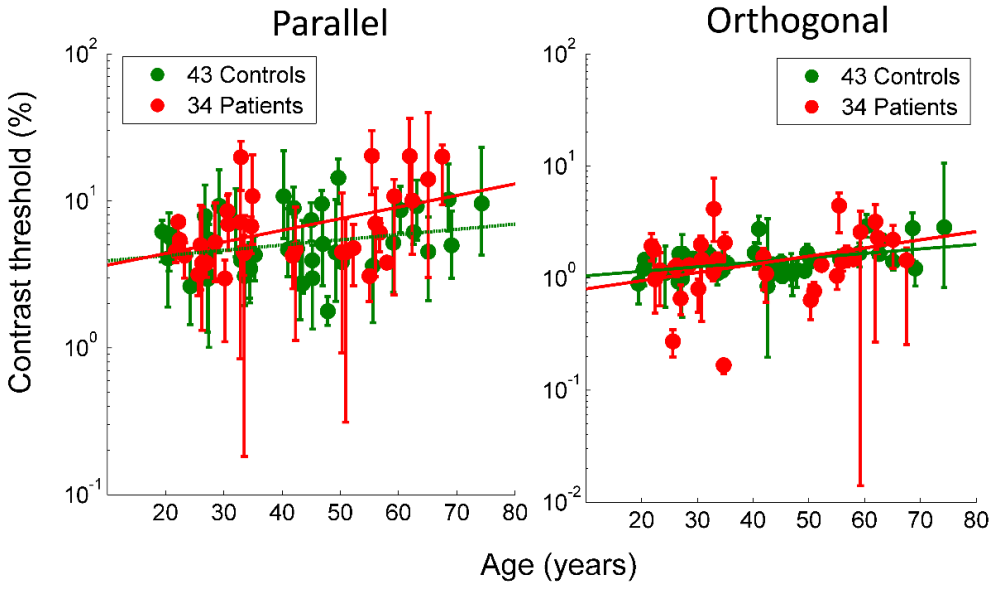


Figure 4.8. Overlaid contrast thresholds of 43 controls (in green) and 34 patients with epilepsy (in red) for the contrast detection task.

Contrast suppression (Equation 2.3) of 43 controls and 34 patients with epilepsy were plotted against age in Figure 4.9. The difference in number of participants between the motion discrimination task and the contrast detection task was due to the fact that smaller number of patients participated in both tasks. Neither patients nor control groups showed a significant relationship with age (p=0.81: in both patients and control groups).

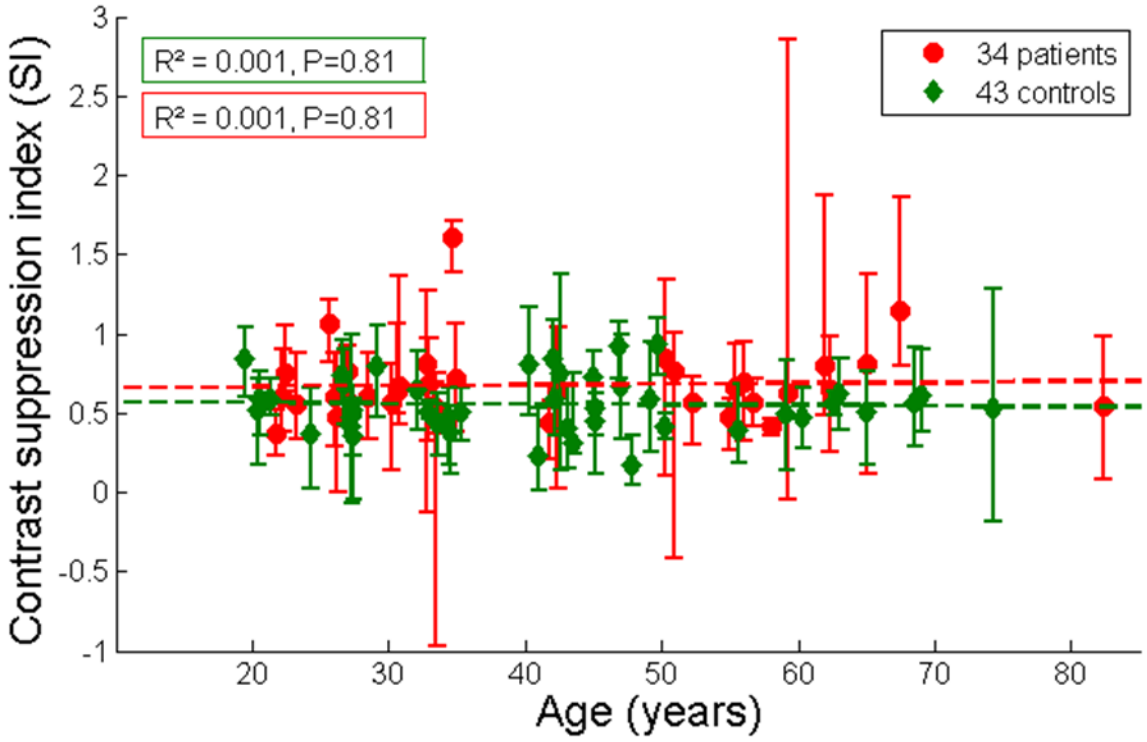


Figure 4.9. Contrast suppression index on the contrast-detection task for 34 patients with epilepsy (red) and 43 healthy controls (green) as a function of age. Error bars show 95% confidence intervals. Dashed lines represent non-significant regression lines between contrast suppression index and age in both controls and patients.

The next stage of the analysis was to see whether visual psychophysics predicted seizure frequency at the group level where patients were devided based on their seizures to five different groups, and ultimately whether it could predict the likelihood of seizures in individual patients.

4.2.3 Analysis of psychophysics data with respect to seizure frequency

As explained before, patients were divided into two different groups of frequent and infrequent seizures according to their seizure frequency starting from 1 to 5 (Table 4.1-Grading A). In order to examine whether results of this grouping were robust, we then plotted the same data but with the shifted threshold between the frequent and infrequent seizures and named it Grading B. Number of patients and healthy participants in each grading is shown in

Figure 4.10. For example, there are 35 patients with frequent seizures and 19 patients with infrequent seizures with 146 healthy controls in grading B.

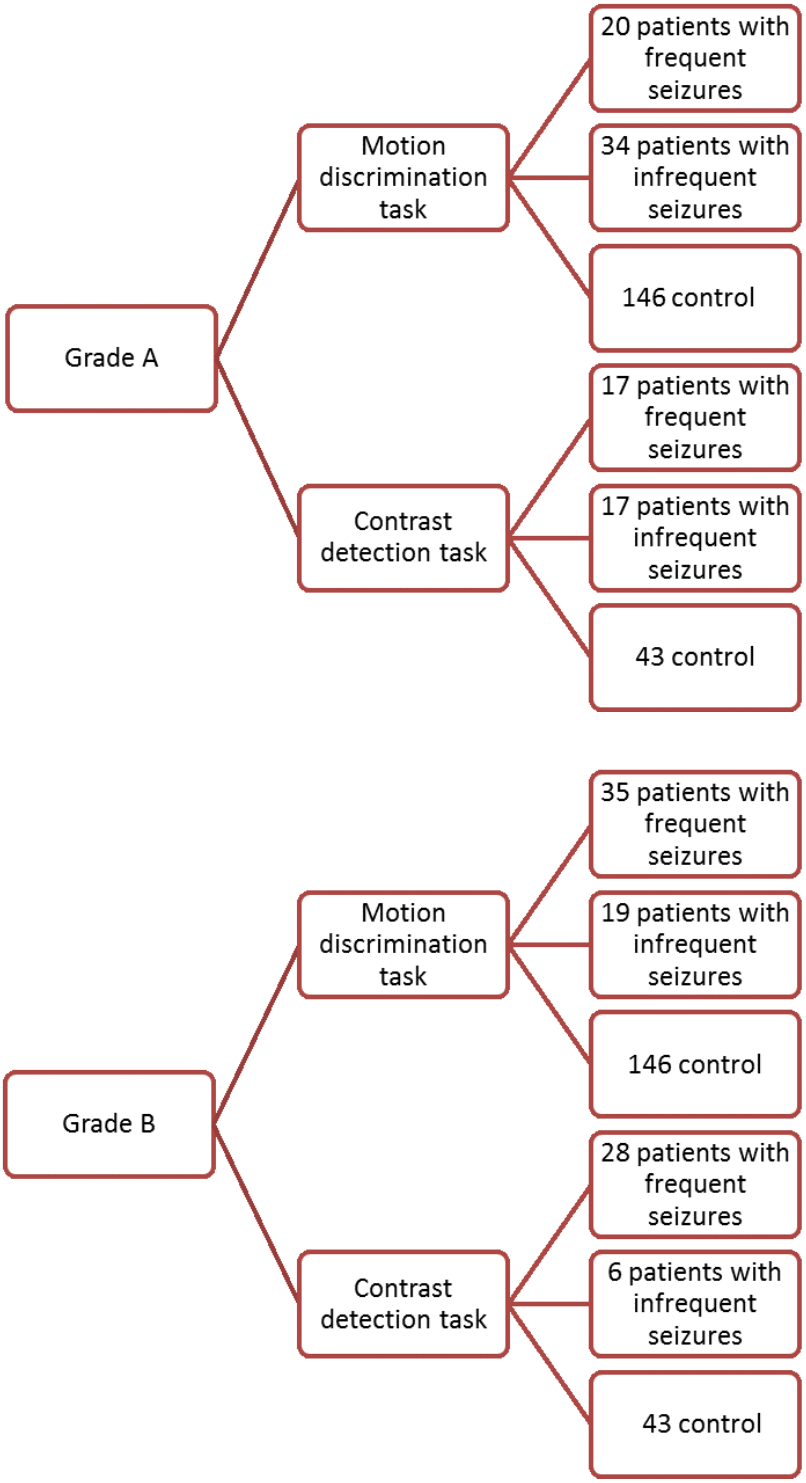


Figure 4.10. Schematic diagram of the distribution of patient groups and healthy participants in Grading A and B for the motion discrimination and contrast detection tasks.

The distribution of data within each group of patients (frequent and infrequent) and healthy controls are demonstrated in Figure 4.11 (Grading A) and Figure 4.12 (Grading B). Lilliefors and Jarque-Bera tests of normality rejected the null hypothesis of data being normal for healthy control participants (p=0.05). Therefore, non-parametric analyses were performed on the groups to compare them against each other. Results are presented in the following sections.

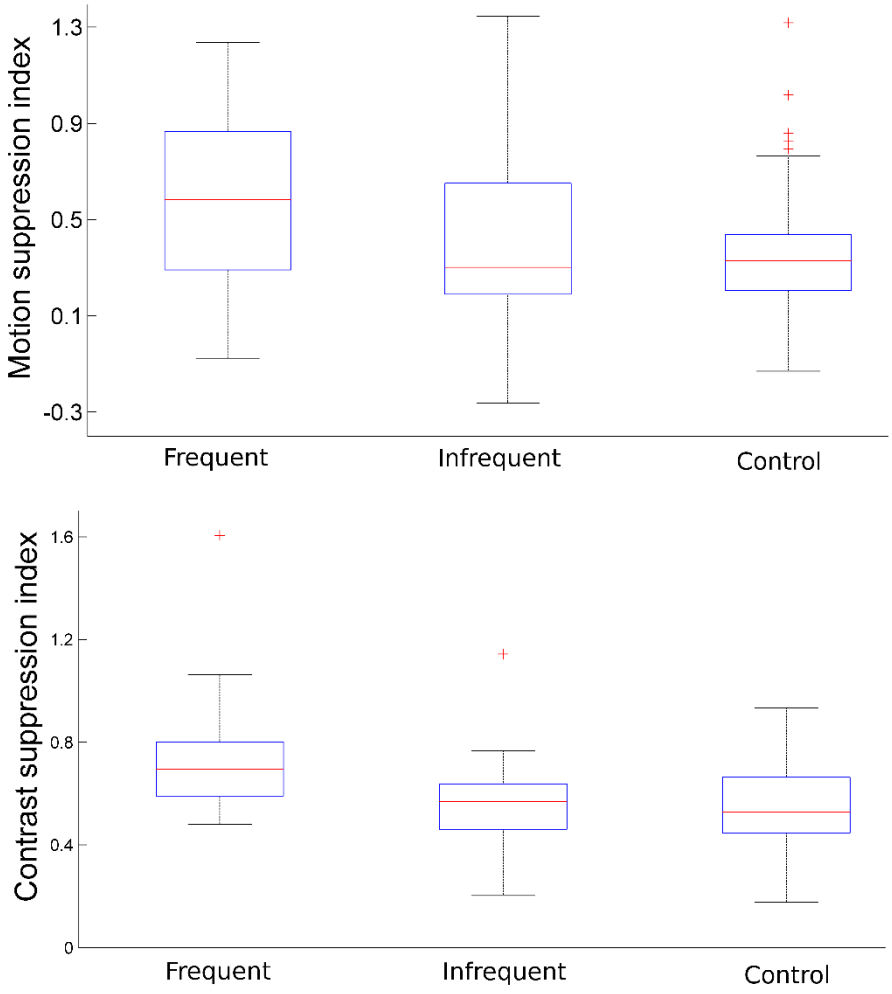


Figure 4.11. Box plot figures of motion suppression and contrast suppression indices for Grading A. The central red mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to show the maximum and the minimum of the data points, and the red plus signs show the outliers.

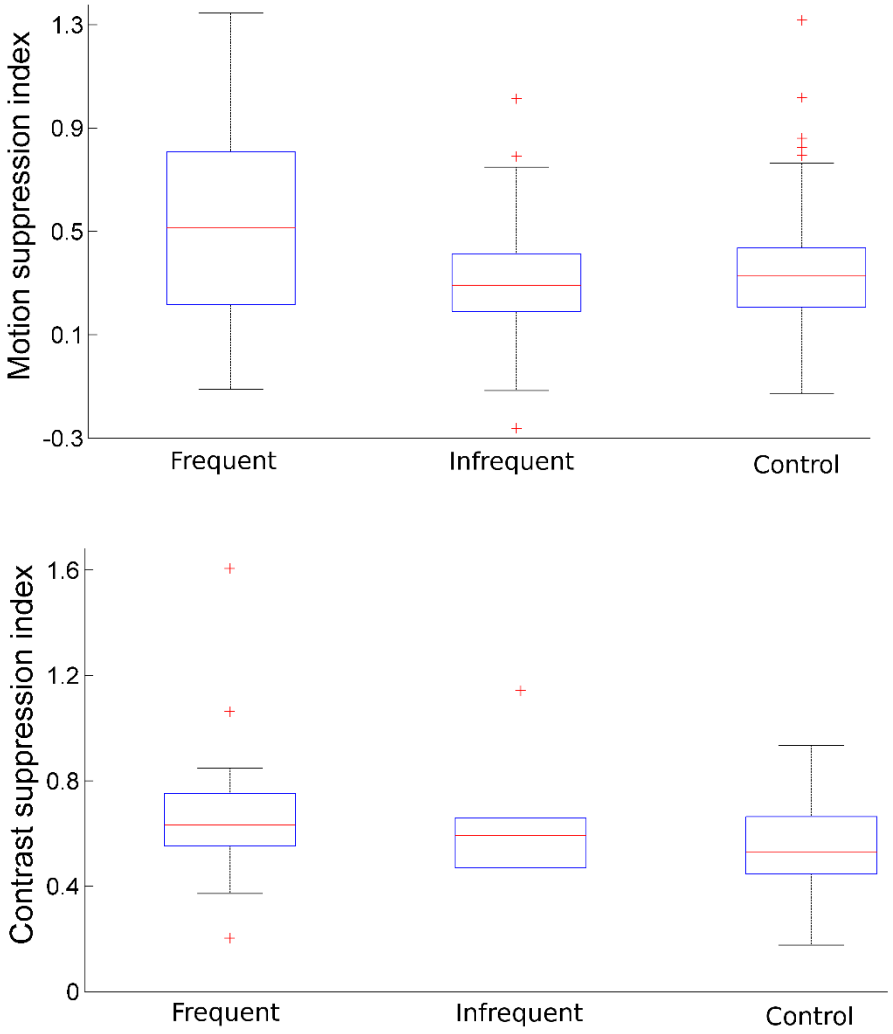


Figure 4.12. Box plot figures of motion suppression and contrast suppression indices for Grading B. The central red mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to show the maximum and the minimum of the data points, and red plus crosses show the outliers.

4.2.3.1 Results of grading A:

The motion discrimination task:

By pooling all the data together, a significant regression equation was found in the motion discrimination task ($F=23.23$, $p<0.001$), with $R^2= 0.1$ (Motion suppression index = -0.0054*Age + 0.573.

Residuals were calculated to check if the linear regression model is appropriate for the motion discrimination task. Then, they were plotted as a function of predicted value of regression analysis to check their variance from line zero (Figure 4.13). The variance of error was not always constant and errors appeared to expand with increase of the predicted value.

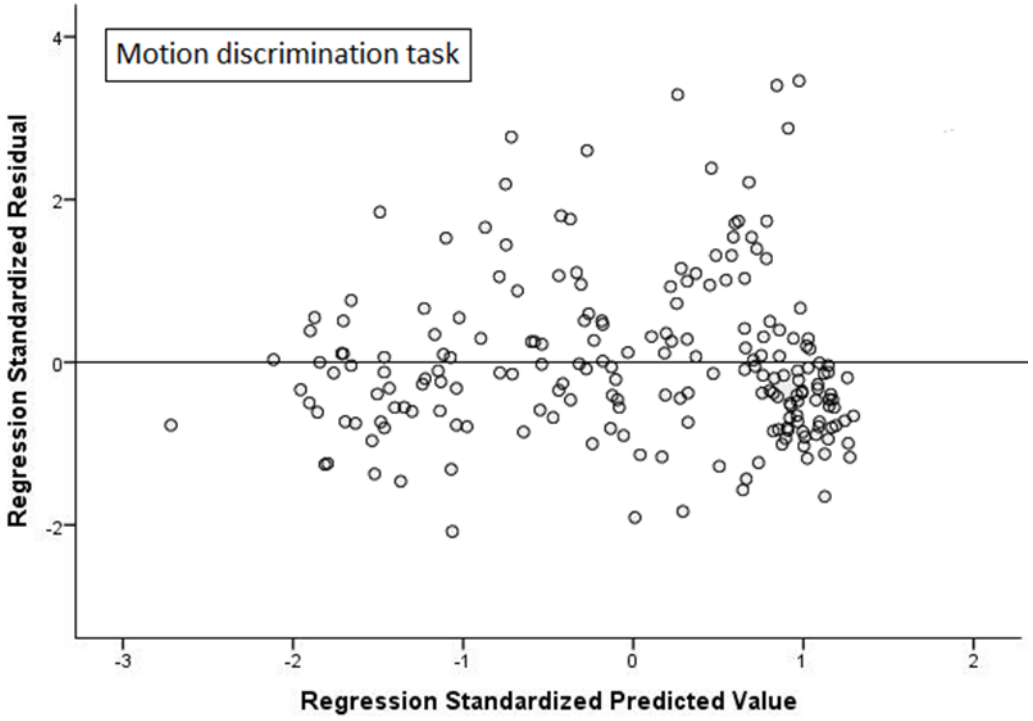


Figure 4.13. Scatter plot of residuals calculated from linear regression analysis for the motion discrimination task. Predicted value by the regression model is on x-axis and the distance from horizontal line y=0 shows how well the model was for each data point (Field, 2013).

To analyse the normality of data, a probability plot (quantile plot or Q-Q) was plotted for all the residuals. Figure 4.14 shows a Q-Q plot for the motion discrimination task. Residuals appeared to be deviated from normality around the beginning and the end of the diagonal line. If data were normal, points would lie on the diagonal line.

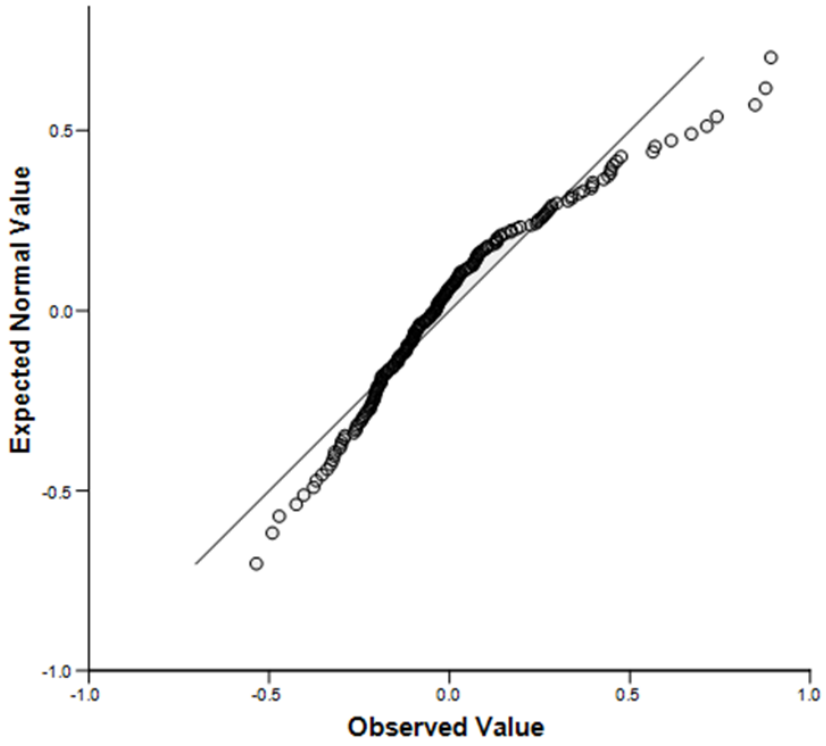


Figure 4.14. Normal Q-Q plot of regression standardized residuals in the motion discrimination task. Black circles represent all residuals. Normally distributed data will lie approximately on the black straight line.

From Figure 4.13 and Figure 4.14, I concluded that non-parametric analysis was more appropriate to apply on the data. Three different non-parametric tests (Analysis of Kruskal-Wallis, Kolmogorov-Smirnov and Mann-Whitney test) were conducted all of which gave similar results.

Analysis of Kruskal-Wallis showed significant difference between the three groups with $p=0.002$ and Chi-Square=12.46. Mann-Whitney test indicated significant difference was between patients with frequent seizures and healthy controls ($p<0.001$, $U=735$), and between patients with frequent seizures and

patients with infrequent seizures (p=0.04, U=226). There was no significant difference between patients with infrequent seizures and healthy participants (p=0.2).

Kolmogorov-Smirnov test (K-S) also confirmed significant difference (Figure 4.15) between patients with frequent seizures (in blue) and healthy controls in grey with p=0.05, although it did not reach significant among the two patients groups.

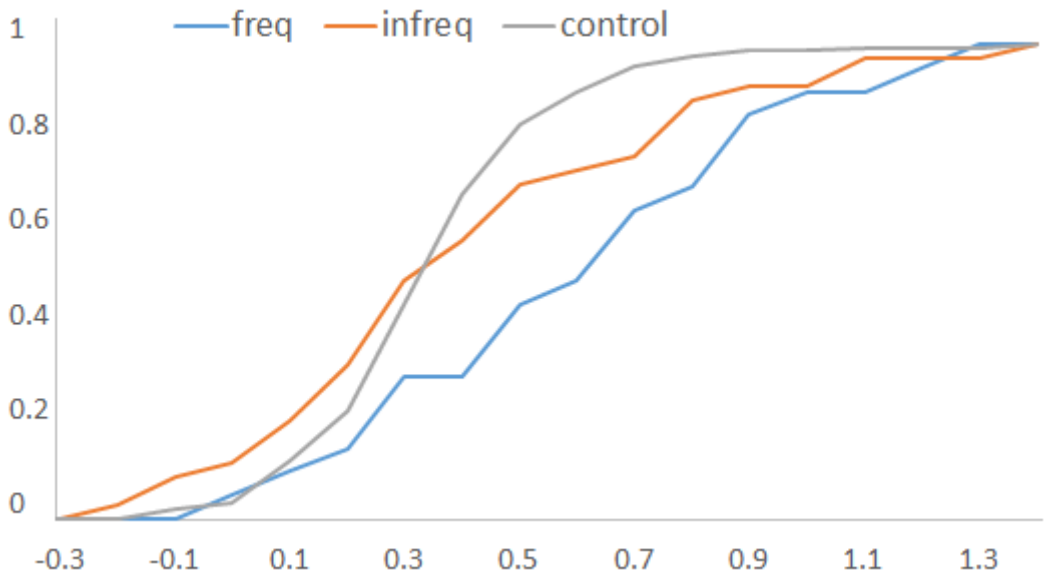


Figure 4.15. Normalised cumulative frequency plots for patients with frequent seizures (in blue), patients with infrequent seizures (orange), and healthy control participants (in grey) for the motion discrimination task in grading A. X-axis shows frequency motion suppression index bins and y-axis is the cumulative frequency.

The contrast detection task:

Analysis of regression in the contrast detection task was non-significant (p=0.87). The Kruskal-Wallis test indicated significant difference between the groups with p=0.006, and Chi-Square=10.24. Mann-Whitney test showed significant difference among patients with frequent and infrequent seizures (p=0.011, U=71), and patients with frequent seizures and healthy controls (p=0.002,

U=179). There was no significant difference between patients with infrequent seizures and healthy controls (p=0.787). Similar results were also observed in Kolmogorov-Smirnov test (K-S) (Figure 4.16, p=0.05).

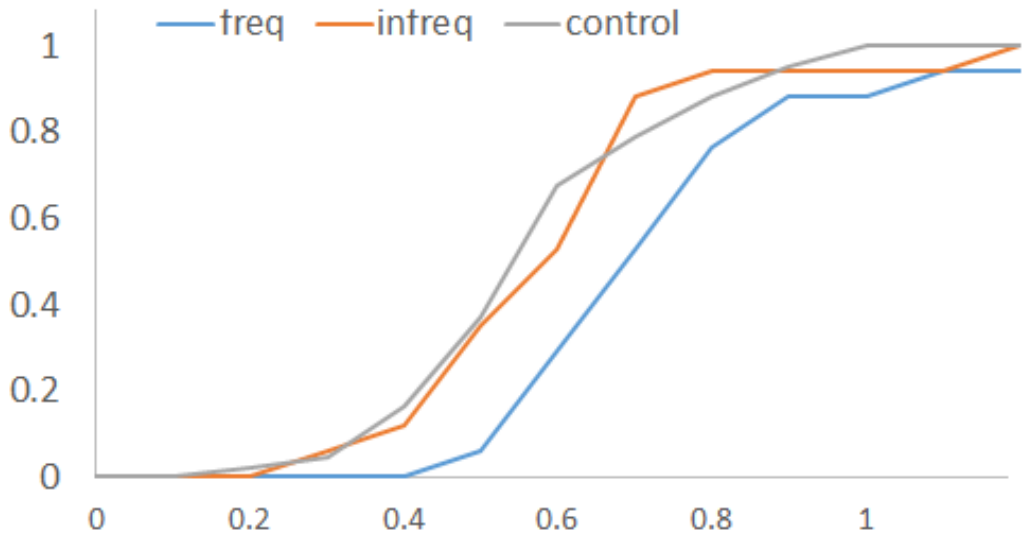


Figure 4.16. Normalised cumulative frequency plots for patients with frequent seizures (in blue), patients with infrequent seizures (orange), and healthy control participants (in grey) for the contrast detection task in grading A. X-axis shows frequency motion suppression index bins and y-axis is the cumulative frequency.

4.2.3.2 Results of grading B:

The motion discrimination task:

Similar non-parametric tests were performed for groups in Grading B where patients with more than or equal to 1 per month are the group with frequent seizures (Table 4.1). The Kruskal-Wallis test showed a significant difference between groups with p=0.001 and Chi-Square=13.15. Further analysis using Mann-Whitney test showed the significant difference was between patients with frequent seizures and healthy control participants (p<0.001, U=1553) and between patients with frequent seizures and patients with infrequent seizures (p=0.024, U=208). No significant difference was found between patients with infrequent seizures and healthy participants (p=0.8).

Further support of the observed difference in the frequent seizure group can be seen in Figure 4.17 which is a normalised cumulative frequency plot for the three groups using the Kolmogorov-Smirnov test (K-S). This plot also confirmed the significant difference between patients with frequent seizures (in blue) and the other two groups (controls in grey, and patients with infrequent seizures in orange) and no significant difference between the controls and patients with infrequent seizures.

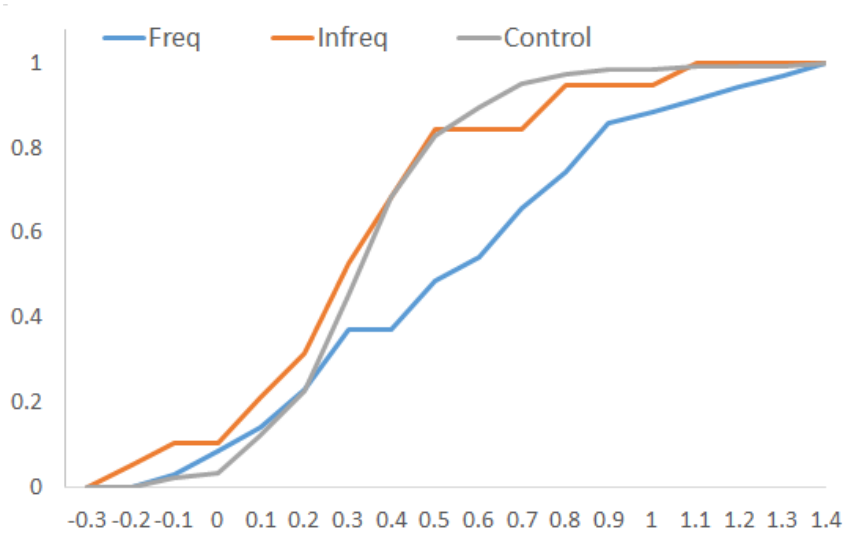


Figure 4.17. Normalised cumulative frequency plots for patients with frequent seizures (in blue), patients with infrequent seizures (orange), and healthy control participants (in grey) for the motion discrimination task in grading B. X-axis shows frequency motion suppression index bins and y-axis is the cumulative frequency.

Moreover, K-S test indicated a significant difference between the overall patients groups and healthy participants at $p<0.005$ shown in Figure 4.18.

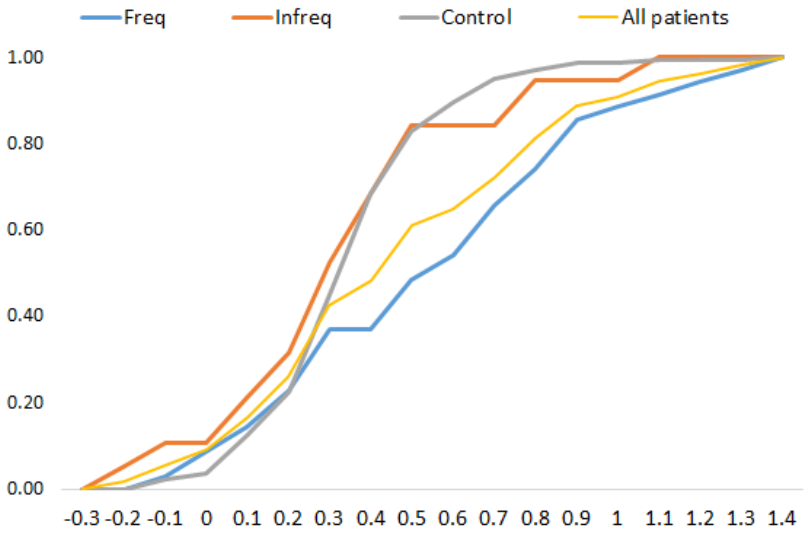


Figure 4.18. A normalised cumulative frequency plots with added distribution for all patients (in yellow) for motion discrimination task. X-axis shows frequency motion suppression index bins and y-axis is the cumulative frequency.

The contrast detection task:

The Kruskal-Wallis and the Kolmogorov-Smirnov tests (K-S) showed no significant difference within the groups in the contrast detection task ($p=0.1$).

4.2.4 Surround suppression is not affected by seizure frequency

To further investigate the differences between patients in regards to their seizure frequencies, individual suppression indices were plotted for each frequency scale in both the motion discrimination and contrast detection tasks in red for the patients and green for the controls (Figure 4.19). Averages of each seizure frequency were then calculated and plotted on each scale (black diamonds).

Age was found to have a significant relationship with the suppression indices in the motion discrimination task. Figure 4.19-top shows motion suppression indices plotted as a function of seizure frequency. Initial inspection of this plot suggested that, in addition to the effect of age, frequency of seizures might also influence the motion suppression indices. We therefore examined the relative importance of this potential predictor along with the factor of age, by performing multivariate regression analyses (Table 4.4). The adjusted R-squared is a modified version of R-squared that has been adjusted for the number of predictors in the model. When considering both age and epilepsy diagnosis together, we found marked increases in the adjusted R^2 values when first subdividing the complete data set (age alone, R^2 = 0105, Table 2) into controls and epilepsy subjects (adjusted R^2 = 0.183). Importantly though, the model was not improved substantially by adding the factor of frequency (adjusted R^2=0.192). Therefore, we concluded that frequency is not a significant predictor of the model.

Multiple regression analysis showed that age and frequency were not significant predictors of the contrast suppression index (age: beta=0.001, t=0.5, p=0.6; grading: beta=0.078, t=1.55, p=0.13). Therefore, there is no relationship between seizure frequency and the contrast suppression index (Figure 4.19, bottom panel).

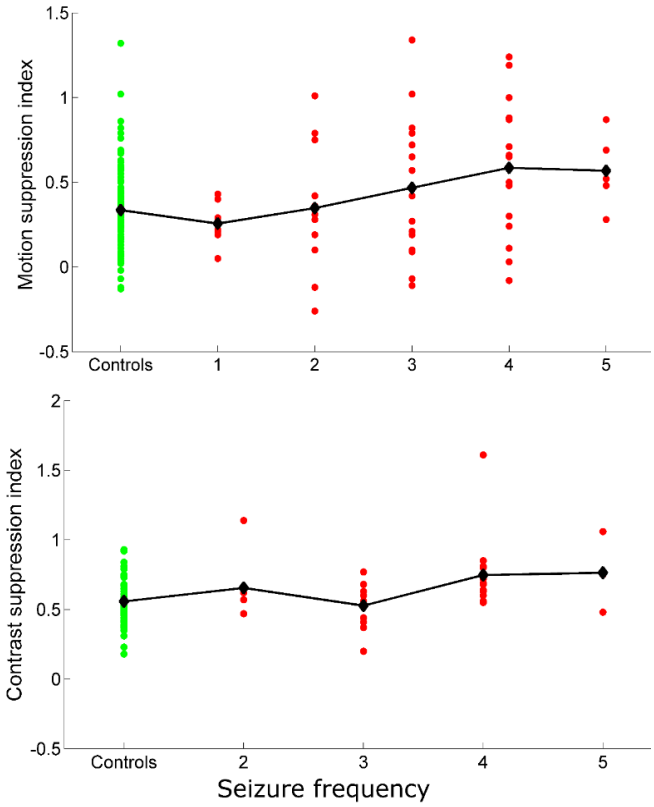


Figure 4.19. Suppression indices for patients (in red) and controls (in green) as a function of seizure frequency. Top panel represents motion suppression and bottom panel contrast suppression indices for individual participants. Black diamonds represent average of suppression index within each seizure frequency scale.

4.2.5 Comparison of patients with a history of generalised seizure and without

SUDEP (Sudden Unexpected Death in Epilepsy) affects approximately 1 in 1000 patients with epilepsy per year, and the single biggest risk factor is the presence of uncontrolled generalised tonic-clonic seizures, increasing the risk to 1 in 150 patients per year (Pack, 2012, Duncan and Brodie, 2011, Nashef et al., 2007).

Patients were divided into three different groups: focal seizures without generalising seizures (F^-, n=24, age range: 22.2-72.5), focal seizures evolving into bilateral convulsive seizures (F^+, n=19, age range: 17.5-82.3) and generalised seizures in the context of a Genetic Generalised Epilepsy (GGE) (n=11, age range: 17-55.4). Details of the individual patients are provided in . The control group is not a normal distribution and therefore data is presented in the form of boxplots (Figure 4.20).

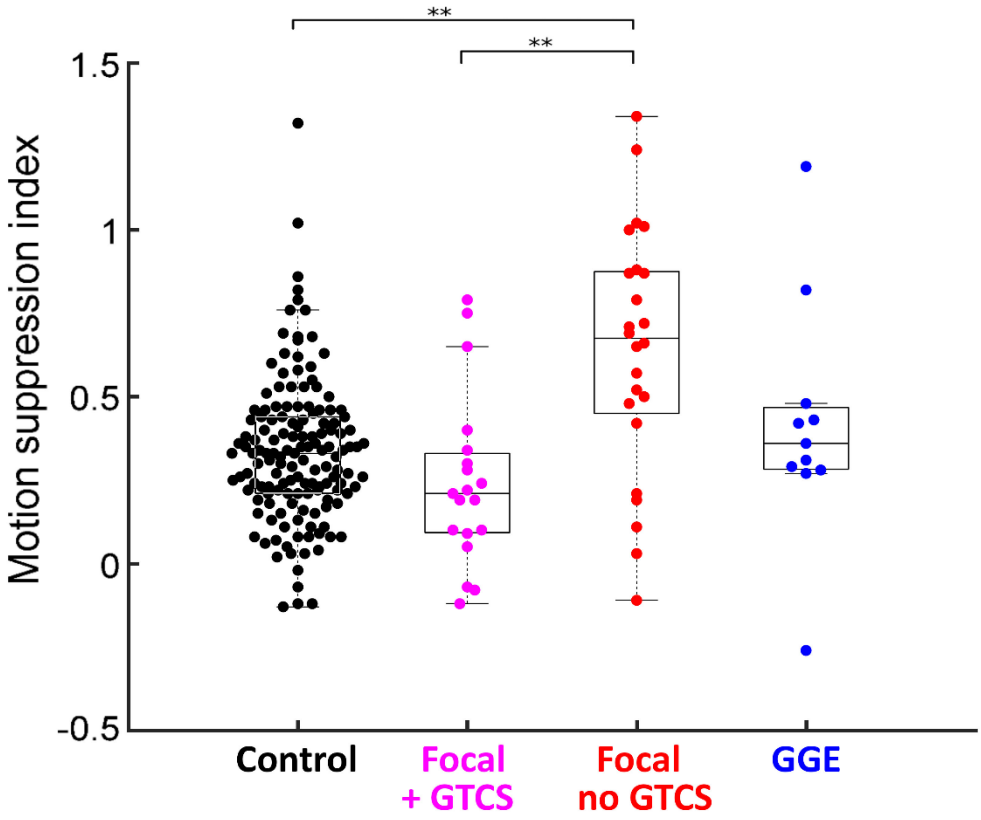


Figure 4.20. Bee swarm boxplots of patients groups and controls. Significance p<0.001 is shown as ** in the figure.

Table 4.3. Individual patient data with respect to their type of seizures

Table 1	idx	Gender	Age (yrs)	Age at onset (yrs)	Duration of epilepsy (yrs)	Presumed location	Seizure frequency	Anti-epileptic drugs	SSI
Focal + GTCS	EP1	M	49	Not known	Not known	Temporal	3	VPA / PHT / CLB / PGB	0.09
	EP5	M	35	34	0.5	Frontal	2	CBZ	0.28
	EP6	F	26	1	>20	Temporal	2	VAL / LTG / PGB / CLB	0.34
	EP12	M	18	17	<1	Occipital	1	none	0.22
	EP13	M	61	27	only 1 seizure	Unknown	3	LTG	0.10
	EP14	F	27	57	>30	Temporal	1	none	0.40
	EP18	F	55	41	<1	Temporal	2	none	0.19
	EP19	M	33	3	14	Possible frontal	4	VPA / CLB / PER / PHT	-0.08
	EP24	F	22	7	>20	Occipital (L)	3	TPM / ZNS	0.19
	EP27	M	68	58	15	Unknown	1	LTG	0.05
	EP30	F	58	11	10	Unknown	3	LEV / PER	0.21
	EP31	F	57	28	30	Temporal	4	LTG / PGB	0.24
	EP33	M	82	51	20	Temporal	3	LTG	-0.07
	EP36	M	59	47	30	Parietal	2	PHT / LTG / LEV / MDZ	0.10
	EP49	F	33	4	>30	Temporal (L)	4	OXC	0.30
	EP51	M	30	17	>25	unknown	2	LTG / TPM	0.75
	EP53	M	33	18	10	Frontal	3	VPA / LEV	0.65
	EP56	M	68	64	>10	Temporal	2	LEV	-0.12
	EP57	M	44	9	9	right hemisphere	3	ZNS / LEV / VPA	0.79
Focal, no GTCS	EP3	M	68	12	>30	Temporal	1	CBZ / LEV / LTG	0.21
	EP4	M	70	64	40	Temporal	4	LTG	0.11
	EP7	F	67	6	8	Temporal	3	PHT / LTG / LEV	-0.11
	EP17	M	42	7	>50	Temporal	3	CBZ / LEV	0.42
	EP20	F	28	11	30	Frontal (L)	5	RTG / CLB / CBZ / LEV	0.87
	EP21	M	52	21	22	Frontotemporal (L)	3	CBZ / LEV	0.72
	EP23	F	62	13	>30	Temporal	4	CBZ / ZNS	0.71
	EP25	F	43	7	30	Temporal	2	ZNS	1.01
	EP26	F	73	54	30	Unknown	1	VPA	0.19
	EP32	M	56	40	15	Temporal	4	LEV / RTG	0.66
	EP34	F	34	21	10	Temporal	4	PER / LEV / PGB	1.24
	EP35	M	22	16	13	Temporal	3	CBZ / TPM / CLB	1.34
	EP37	F	27	23	4	Temporal	4	PER	1.00
	EP38	F	25	0	4 yrs	Multifocal	4	LEV / LTG / CLB	0.88
	EP39	M	34	31	>20	Temporal	5	TPM / LTG / OXC	0.69
	EP41	M	26	16	3 yrs	Temporal	5	CLB / LCM / LEV / ZNS	0.52
	EP42	F	31	6	>10	Temporal	3	LTG / PGB	1.02
	EP44	M	42	14	>20	Fronto-temporal	4	VPA / LTG	0.50
	EP45	M	35	11	28	Frontal	4	VPA / PGB / ESL / PB	0.48
	EP46	F	31	5	>20	temporal lobe	4	PGB / LEV / CBZ / PHT / CLI	0.65
	EP47	M	50	45	>25	Anterior temporal (L)	4	ZNS	0.87
	EP48	F	62	46	6	Temporal	4	CBZ / CLB / VPA	0.03
	EP50	F	26	22	>40	Temporal	2	none	0.79
	EP55	M	51	36	~4	Temporal	3	LEV	0.57
GGE	EP8	F	41	~5	2	Generalised	5	none	0.48
	EP9	M	18	12	30	Generalised	1	VPA	0.43
	EP10	M	17	16	5	Generalised	2	VPA	0.31
	EP11	M	55	54	0.5	Unknown	2	VPA	0.42
	EP15	M	22	22	<1	Generalised	2	none	0.36
	EP16	M	18	17	1	Generalised	1	none	0.29
	EP22	F	29	20	8	Generalised	3	LEV	0.82
	EP28	M	51	~5	30	Generalised	3	VPA / LEV / CBZ	0.27
	EP29	F	23	11	10	Generalised	4	ZNS	1.19
	EP40	F	22	22	<1	Generalised	5	LEV	0.28
	EP43	F	55	15	>30	Generalised	2	PRM / PGB	-0.26

Frequency gradin	
<1 / year	1
<1 / month	2
<1/ week	3
<1 / day	4
>1 / day	5

The motion suppression index is dependent on age as was shown in chapter 4, Figure 4.6.

Figure **4.21** shows the relationship between each group of participants as a function of age with corresponding regression lines. The distribution of SSI values

differed significantly between the four groups (F^+ (Focal+GTCS), F^- (Focal no GTCS), GGE and controls; ANOVA, $F_{(3,196)} = 11.66$, $p < 0.0001$; Figure 4.20), with post hoc t-tests indicating that the F^- group was the outlier. The previously noted regression with age was apparent for each subgroup individually (

Figure **4.21**), although this was only significant for the two larger sample groups, F^+ ($n = 19$, $R^2 = 0.259$, $p < 0.05$) and F^- ($n = 24$, $R^2 = 0.527$, $p < 0.001$) but not for GGE. To examine the relative importance of this potential predictor along with the factor of age, multivariate regression analyses (Table 4.4) were performed. We found marked increase in the adjusted R^2 value in a model of suppression index-age after subclassifying into the F^+, F^- and GGE subtypes (adjusted $R^2 = 0.318$, Table 4.4).

Importantly though, the age and subtype model was not further improved by adding the seizure frequency (adjusted $R^2 = 0.315$, Table 4.4). This lack of effect of seizure frequency was better appreciated when this predictor was plotted for the three seizure subtypes individually (Figure 4.22). These plots also show that in our samples, the F^- patients tended towards a higher seizure frequency. This mismatch in the seizure frequency between the groups can explain the increase in R^2 going from a model using just "Age" to one using "Age + Frequency" (Table 4.4): in this case, in which seizure subtype was ignored, the subtype acts as a hidden predictor and distorts our interpretation of the effect of frequency. The important comparison is that a model using all three predictors actually explains no more of the variance than one using just age and seizure subtype.

The regression table for the three-predictor model indicates highly significant p values for the control intercept and slope ($p << 0.001$), and for the change in intercept and slope for the F^- group ($p << 0.001$), but for no other comparison, and notably frequency was non-significant ($p = 0.632$). We conclude, therefore, that

only age and seizure subtypes were significant predictors of motion suppression index.

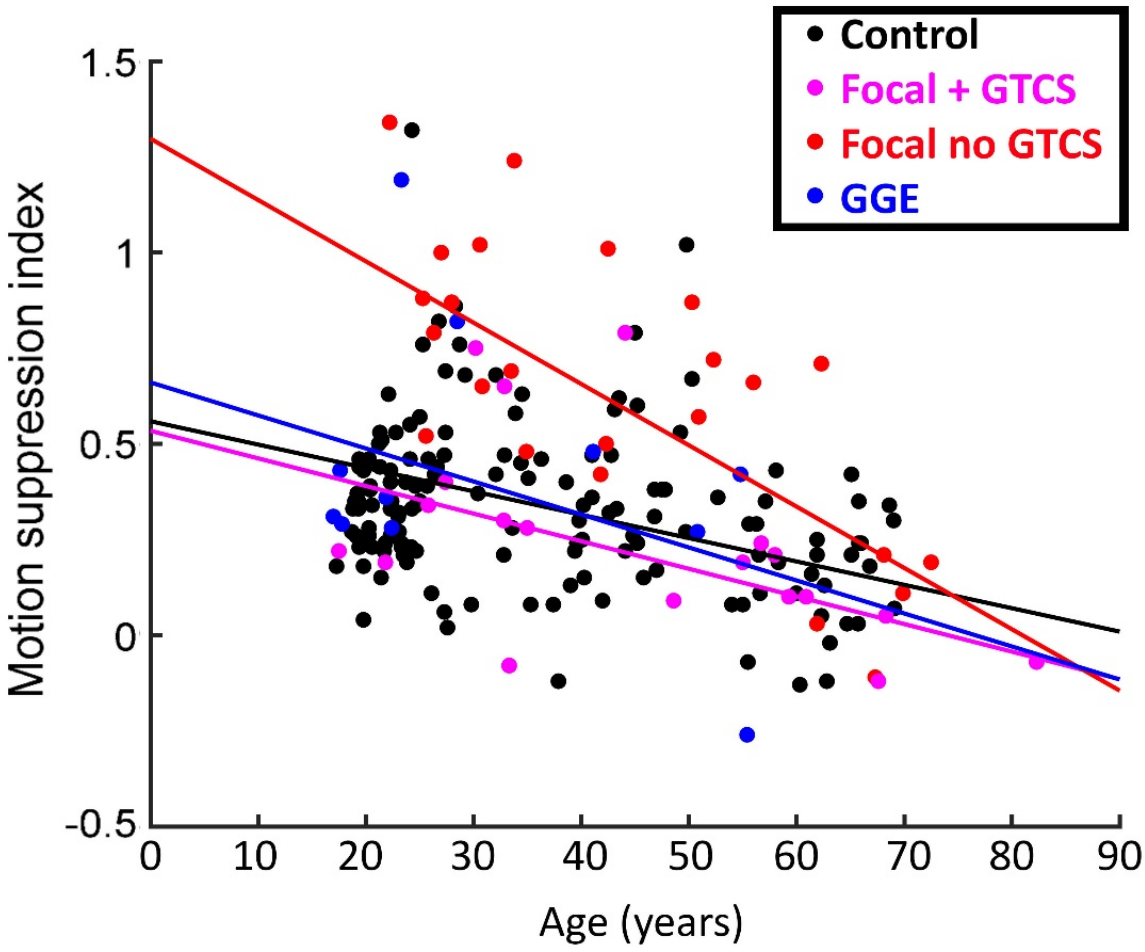


Figure 4.21. Motion suppression index of patients and controls as a function of age. Patients with focal seizures are shown in red, with focal seizures evolving into bilateral convulsive seizures in magnet, with GGE in blue and controls in black. Solid lines show where the regression with age was significant.

Table 4.4. Model comparisons. The optimal model is indicated by *, and the parameters for that model (**, P << 0.001). Note that for the Control group statistics, what is being tested is significant difference from zero, and for the other groups, it is the significant difference from the controls.

Models		R^2	Adjusted R^2
SSI vs	Age	0.105	-
	Age, Epilepsy	0.195	0.183
	Subtype, Freq	0.170	0.144
	Age, Freq	0.200	0.192
	Age, Subtype	0.342	0.318 *
	Age, Subtype, Freq	0.342	0.315

Model parameters (Age, Subtype)

	Gradient (yr^{-1})	Intercept
Controls	-0.0041 +/- 0.0011 **	0.484 +/- 0.047 **
F+	-0.0071 +/- 0.0031	0.566 +/- 0.147
F-	-0.0164 +/- 0.0031 **	1.362 +/- 0.141 **
GGE	-0.0088 +/- 0.0047	0.694 +/- 0.167

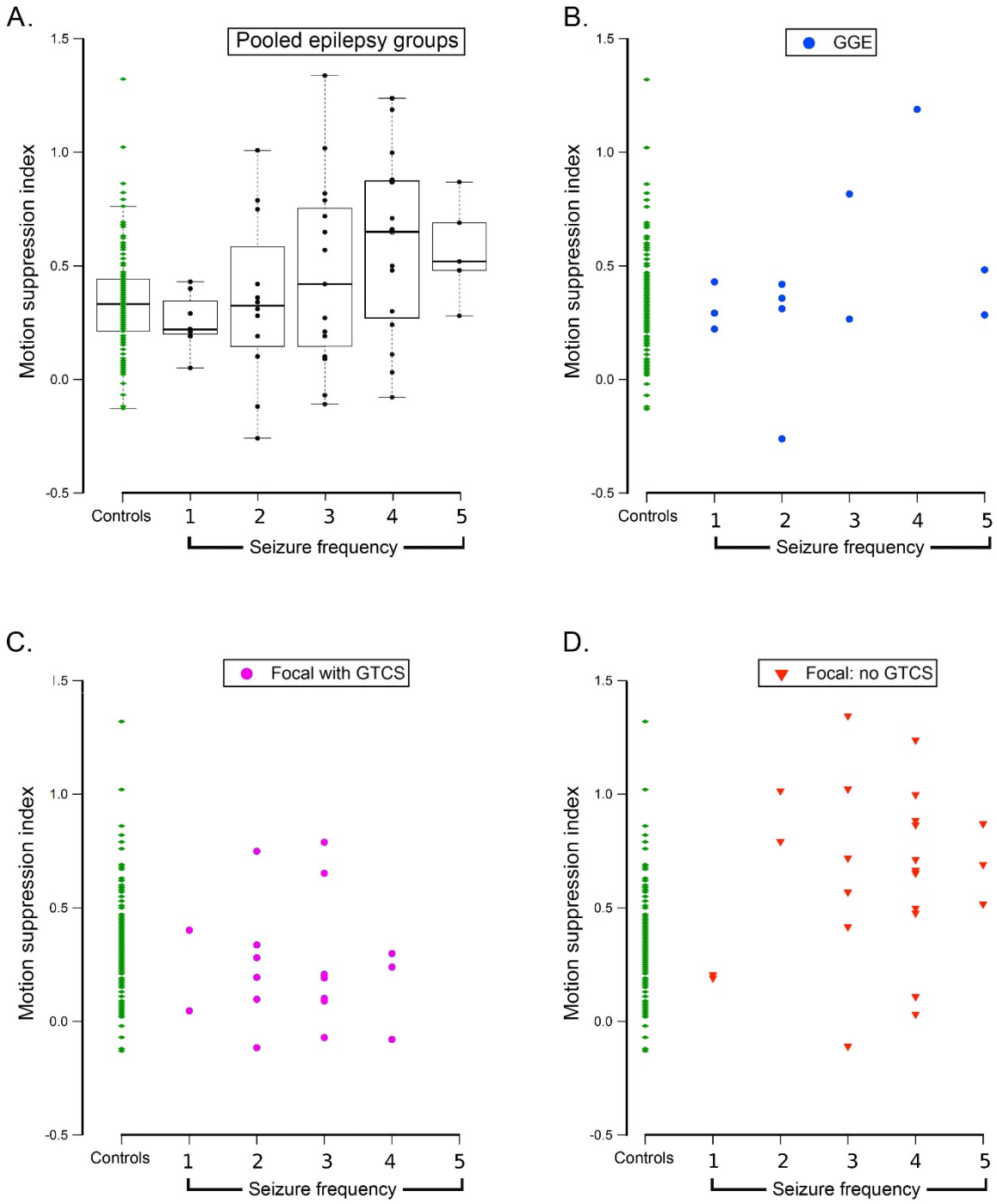


Figure 4.22. Boxplots of the suppression indices with respect to frequency of seizures for the pooled epilepsy cohorts, and for each of the three subgroups of epilepsy patients, plotted separately (B-D, all non-significant).

4.2.6 No significant effect of anti-epileptic drugs on motion suppression indices

There are a number of factors affecting cognition in patients with epilepsy, for instance age of onset, aetiology of seizure, seizure frequency, severity and duration of seizures, as well as epilepsy treatment or anti-epileptic drugs (Motamedi and Meador, 2003, Loring et al., 2007, Carpay et al., 2005). Certain anti-epileptic drugs (AEDs) are one possible confounding parameter to interact with the GABAergic system, and indeed this is presumed to contribute to their clinical effect (Walker and Surges, 2009). One of the reasons of high prevalence of psychosocial problems within patients with epilepsy in spite of the fact that most have normal intelligence, is the possibility of negative influence of AEDs (Drane and Meador, 1996, Kalviainen et al., 1996, Kwan and Brodie, 2001). For instance, in a monotherapy study on 110 patients with epilepsy treated with Carbamazepine (CBZ), Sodium Valproate (VPA) and Phenytoin and 24 controls, Carbamazepine treated patients showed poorer psychomotor scores than controls and Sodium Valproate treated patients ($p<0.05$), and Phenytoin treated patients scored less well on the composite memory scale compared to other groups (Gillham et al., 1990). A study on children with epilepsy treated with Phenobarbital done by Sulzbacher et al. (1999) showed the adverse effects of Phenobarbital on language skills and worsening of behavioural disorders. Other examples are in patients treated with Benzodiazepines, Clonazepam and Clobazam, which can cause cognitive impairment and sedation (Dichter and Brodie, 1996, Kwan and Brodie, 2001). A study on patients treated with Topiramate found significant decline in measures of attention and word fluency at acute doses (Martin et al., 1999). Another study on patients treated with Zonisamide showed mild degrees of abnormal thinking and impaired verbal learning (Berent et al., 1987, Kwan and Brodie, 2001). We have rather poor understanding of how antiepileptic drugs (AEDs) work (Macdonald and Kelly,

1995), but it is reasonable to assume that some will affect inhibitory processes, including Sodium valproate, Clobazam, Zonisamide, Retigabine, Topiramate, Primidone, and Phenobarbital. Valproate Acid (VPA) may enhance GABA mechanisms through the synthesis of GABA by stimulating GAD enzyme (glutamic acid decarboxylase). A study using voltage clamp recordings demonstrated that VPA selectively modulates the voltage dependence of sodium current steady-state inactivation and reduces cellular excitability (Taverna et al., 1998, Vreugdenhil and Wadman, 1999). Clobazam is a $GABA_A$ receptor agonist and may influence voltage-sensitive conductance of calcium ions and the sodium channels (Sankar, 2012). Phenobarbital has a direct action on $GABA_A$ receptors which prolongs the duration of chloride channel opening (Polc, 1982). Topiramate might enhance GABA through increase of Chloride influx (White et al., 1997). Zonisamide increases GABA-mediated inhibition (Wilfong and Willmore, 2006) and Retigabine increases inhibitory neurotransmission via a direct influence on the $GABA_A$ receptor (van Rijn and Willems-van Bree, 2003, Otto et al., 2002).

Therefore, the pattern of medication of all the patients (total of 54) were analysed. Collectively, patients were on 17 different medications (Table 4.5). Seven patients were recruited at the time of diagnosis and were not therefore on medication when they did the psychophysical tests, 18 patients were on monotherapy, and the rest were on multiple drugs (Figure 4.24, A).

Table 4.5. Subdivision of the drugs into those that are known to affect the GABAergic system, and those that are thought to have their effect independent of GABA.

No documented GABA effect	CBZ	Carbamazepine
	ESL	Eslicarbazepine
	LCM	Lacosamide
	LEV	Levetiracetam
	LTG	Lamotrigine
	OXC	Oxcarbazepine
	PER	Perampanel
	PGB	Pregabalin
	PHT	Phenytoin
Known GABAergic interactions	CLB	Clobazam
	MDZ	Midazolam
	PB	Phenobarbital
	PRM	Primidone
	RTG	Retigabine
	TPM	Topiramate
	VPA	Valproic Acid
	ZNS	Zonisamide

The GGE patient group tended to be on a lower numbers of drugs, with the F^+ and F^- groups taking similar numbers (1.84 and 2.33 respectively). The most commonly prescribed drugs were levetiracetam (19 patients), lamotrigine (14 patients) and sodium valproate (13 patients), but notably the pattern of drug prescriptions for the patients with generalised seizures (GGE and F^+) and those without (F^-) were broadly similar (Figure 4.24, B).

Since the psychophysics test is presumed to reflect cortical GABAergic function, we subdivided the epilepsy cohort into two groups according to whether or not they were on drugs that are known to interact with GABA (Table 4.5; note that both groups contain people on polypharmacy). Notably, there was no difference in the SSI for these two groups (Figure 4.23, Non- GABA drug group, n = 27, SSI = 0.40 +/- 0.37; GABA group, n = 27, SSI = 0.49 +/- 0.36).

Furthermore, including the presence or absence of drugs with GABAergic effects as a predictor in the regression analyses did not explain any additional variance (adjusted R^2 =0.316). This was also true when the regression analyses were restricted to the epilepsy subjects (age / epilepsy subtype, adjusted R^2 = 0.475; age / epilepsy subtype / GABA effect, adjusted R^2 = 0.464).

Finally, we examined whether patients with low versus high SSI scores (subdivided at the median SSI) were predominantly within the GABAergic / non-GABAergic drug interactions groups (Figure 4.24). There was no significant difference between the low and high SSI patients (Fisher's exact tests), either for all the patients pooled irrespective of seizure type, nor for the generalised and focal groups alone. We concluded, therefore, that drug interactions do not underlie the effects of seizure type and age on the surround suppression index.

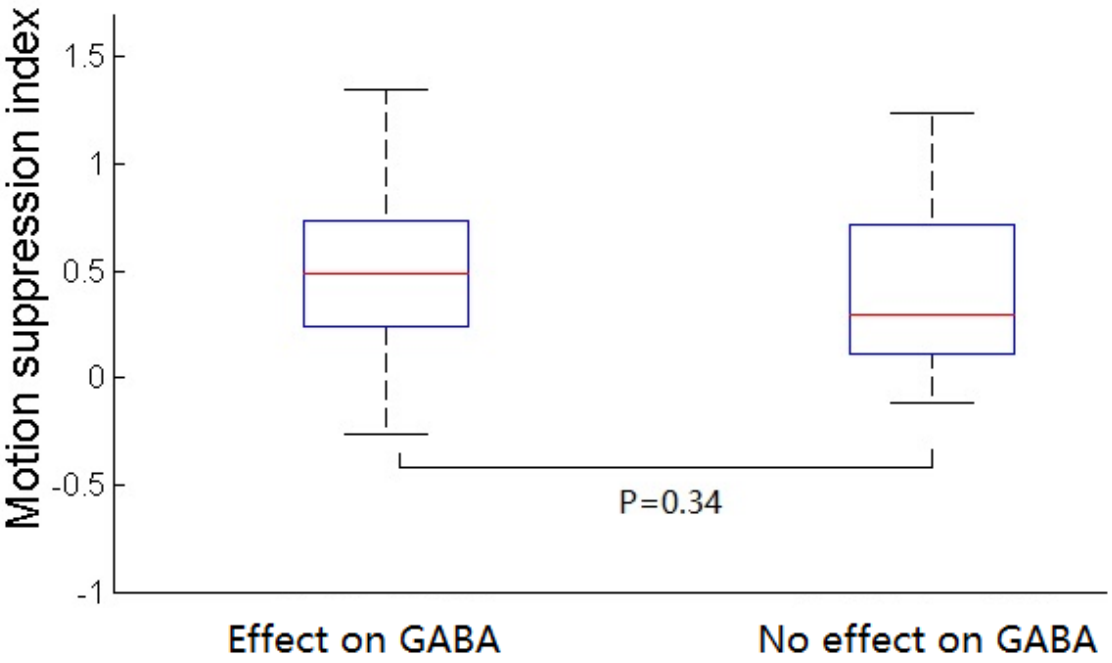


Figure 4.23. Boxplot of motion suppression index of patients with epilepsy in two groups of patients who used AEDs known affecting GABA and not affecting GABA. P value and number of patients in each box plot are shown.

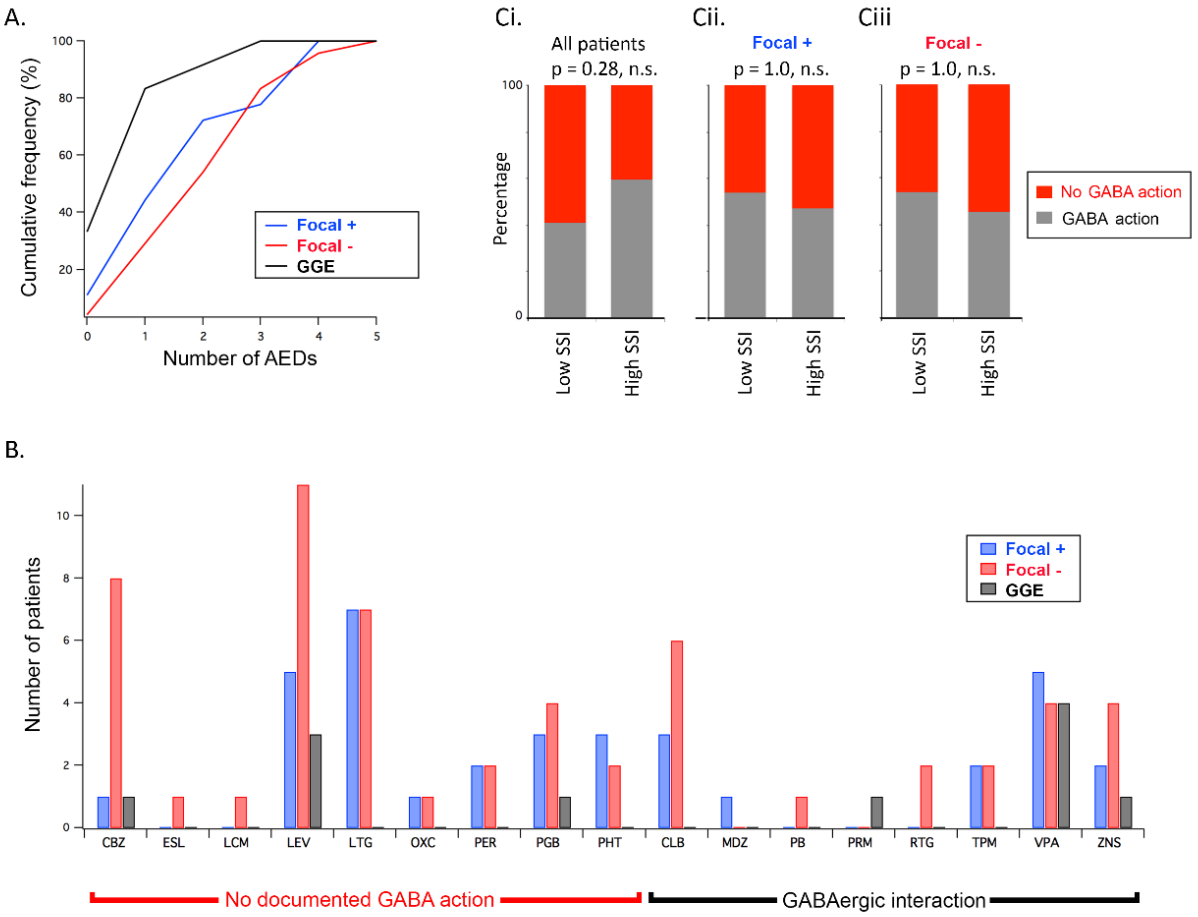


Figure 4.24. Patterns of medication for the three subgroups in the patient cohort. (A) Cumulative frequency plots of the proportions of the patients in the three groups taking different numbers of anti-epileptic drugs (AEDs). (B) Histogram showing the numbers of patients in each group taking the different AEDs. The abbreviations of the drugs are given in Table 4.5. (C) Proportions of patients with either low SSIs or high SSIs who are on medication that either interacts with, or is considered independent of, the GABAergic system. In each case, the cohort was subdivided at the median score SSI (Ci, all patients, n = 27 for both low and high SSI groups; Cii, patients with generalized epilepsy (F^+ and GGE), n = 15 for both groups; Ciii, patients with exclusively focal epilepsy (F^-), n = 12 for both groups).

4.3 Discussion

The relationship between excitation and inhibition has an important role in maintaining proper dynamics of neuronal networks in the cortex (Douglas et al., 2003, Buzsáki, 2011). Concurrent rises in excitation and reduction in inhibitory forces has been shown to produce pathological conditions such as epilepsy (Dichter and Ayala, 1987). Recent studies have demonstrated the important role of GABAergic inhibition on cortical processing at single cell and network level where inhibition has an influence on setting the state of the network and cortical oscillation (Alitto and Dan, 2010).

To explore the idea of using visual psychophysics as a way of measuring the quality of surround suppression, first differences between patients with epilepsy and healthy participants were investigated. In epilepsy the number of seizures is an important factor in determining the severity of epilepsy. Therefore, patients were divided to five category based on their seizure frequency (Table 4.1). In fact, Figure 4.19 showed that patients with no seizures or less than one in a year (group1) did not show any difference in their suppression index to healthy controls. We then defined two grading: Grading A included patients with more than one seizure per week as frequent, while grading B included those with more than one seizure per month as frequent. These cut-offs are arbitrary and were chosen to give us a consistent grouping for patients' frequency of seizures. In addition, a lot of patients could not give precise information on their number of seizures. Therefore, Grading A and B with two different cut-offs (for example: more than 1 seizure per week versus more than 1 per month) gave us the opportunity to show whether the results in any of the tasks were robust. However, with limit of time we did not investigate other cut-offs which are worth investigating, such as those who are in remission and those with less than one seizure per month.

Figure 4.19 indicated that the average of motion surround suppression tends to escalate with the increase of seizure frequency in the motion discrimination task. However, further investigation showed that patients with exclusive focal seizures tended towards a higher seizure frequency (Figure 4.22). This mismatch in the seizure frequency between the groups can explain the subtle increase in R^2 going from a model using just "Age" to one using "Age + Frequency (Table 4.4). In the case, in which seizure subtype was ignored, the subtype acts as a hidden predictor and distorts our interpretation of the effect of frequency. The important comparison is that a model using all three predictors actually explains no more of the variance than one using just age and seizure subtype. The lack of effect of seizure frequency was clearer when this predictor was plotted for the three seizure subtypes individually (Figure 4.22). We conclude, therefore, that only age and seizure subtypes were significant predictors of the motion suppression index.

It is important to remember that although visual psychophysical methods measure surround suppression in the occipital lobe, we think that the produced suppression index measured for each person either by the motion discrimination or the contrast detection tasks is an indication of the global quality of the inhibitory mechanisms. In other words, patients with a focal epilepsy, as well as having a focal excitation, may have a global inhibitory impairment (Trevelyan and Schevon, 2012). For instance, the calcium-binding protein Parvalbumin (PV) plays an important role in the regulation of local inhibitory effects applied by GABAergic interneurons on pyramidal neurons and Parvalbumin deficiency results in increased susceptibility to epileptic seizures (Schwaller et al., 2004). Therefore, it might be reasonable to hypothesise that the observed elevated baseline of inhibition in patients with epilepsy, especially in those with more frequent seizures, exists to oppose the possibility of increase of activity in an

over excited network, compared to healthy controls or patients with less frequent seizures. How and why exactly this antagonism mechanism fails and leads to a seizure propagation is still not clear. Some studies have shown evidence of interneurons not firing (Cammarota et al., 2013a), perhaps due to a depolarising block (Ziburkus et al., 2006). In addition, there is evidence of a short term depression through presynaptic inhibition, GABAergic vesicular depletion, post synaptic desensitization (Trevelyan and Schevon, 2012), and increase of postsynaptic chloride (Thompson and Gahwiler, 1989a, Thompson and Gahwiler, 1989b, Ellender et al., 2014, Fujiwara-Tsukamoto et al., 2010). Further analysis of covariates (ANCOVA) indicated a significant difference in motion suppression index between healthy controls and patients with higher number of seizures (namely group 3 and 4, $p<0.005$). Moreover, patients with less number of seizures were significantly different compared to those with higher number of seizures. These findings are in line with the non-parametric tests that were done in grading A and B.

Another interesting finding was the existence of very long duration thresholds in the motion discrimination task (over 800ms) only in patients with epilepsy (Figure 4.3 A and Figure 4.4). All of these patients had frequent seizures and more than half of them had twice higher duration thresholds in small patterns relative to average patients. It is not clear why these patients exhibited these very long duration thresholds. Some of them showed some degree of confusion in identifying the moving direction in large high contrast, however they had no problem for the small high contrast task. Thresholds with this intensity have never been published in other studies to our knowledge.

Similar to the control subjects' data presented in chapter 3, age was a significant factor in the motion discrimination task in patients. And, the fact that contrast suppression did not display any correlation with age is additional evidence

pointing to the fundamental differences within these two paradigms (Yazdani et al., 2015).

Anti-epileptic drugs (AEDs) could be a possible confounding factor to affect neuronal networks by suppressing excitation or enhancing inhibition. Therefore, it was plausible for this to be a reason of observed differences in patients' groups. There are a vast number of studies on the negative effects of AEDs on the visual performance often on patients with prolonged AED use (Roff Hilton et al., 2004, Verrotti et al., 2007, Steinhoff et al., 1997b). Examples of these disturbances are mild diplopia, blurred vision and nystagmus. Some studies have presented data supporting that GABAergic and glutamatergic neurotransmission may be mediators of retinal signal transmission (Steinhoff et al., 1997a, Slaughter and Bai, 1988). One study has linked AEDs such as Vigabatrin and Carbamazepine with reduced contrast sensitivity (Nousiainen et al., 2000). None of the patients in my study reported any visual deficit. Colour perception was assessed in some patients using Ishihara test and was found to be normal. It is important to note that the stimuli in high contrast (92%) is way above the threshold for someone with normal contrast sensitivity, but not for someone with impaired contrast sensitivity. Here patients were not contrast impaired in general because the mean of the contrast threshold in orthogonal condition for controls and patients were very close (controls: 1.47 and patients 1.67). Analysis of Student's t test showed that the two are not significantly different with t=-1.1, df=75 and p=0.3. On the other hand, the mean of the contrast threshold in parallel condition is higher in patients than in controls (t=-2.2, p=0.021), consistent with higher surround suppression, but within-subject comparison by computing the surround suppression index, showed this not to be significant. Therefore, its relevance is unclear. Since the psychophysics test is presumed to reflect cortical GABAergic function, we subdivided the patients into two groups

according to whether or not they were on drugs that are known to interact with GABA (Table 4.5). There was no difference in the SSI for these two groups. Furthermore, including the presence or absence of drugs with GABAergic effects as a predictor in the regression analyses, did not explain any additional variance (adjusted R^2 = 0.316). This was also true when the regression analyses were restricted to the epilepsy subjects. In addition, the pattern of drug prescriptions for the patients with generalised seizures (GGE and F^+) and those without (F^-) were broadly similar (Figure 4.24, B). We concluded, therefore, that AEDs interactions do not underlie the effects of seizure type and age on the surround suppression.

We next sub-grouped the epilepsy group with respect to seizure type (Berg et al., 2010). Patients with focal epilepsy and a history of a generalised tonic-clonic seizure were compared with focal and GGE (Figure 4.20 and

Figure **4.21**). Interestingly, regression and analysis of ANOVA showed a clear difference between patients with exclusive focal seizures and all the other groups ($p<0.001$). Our original hypothesis had been that people with epilepsy would have a reduced SSI, indicative of lowered inhibitory restraint. Instead, results indicated that patients with generalised seizures are not different from control subjects, but those with focal epilepsy that does not generalise (F^-), have a raised SSI. This surprising finding contrasts with the reduced SSI in other groups: people with schizophrenia (Tadin et al., 2006), depression (Golomb et al., 2009), low IQ (Melnick et al., 2013) and aged subjects (Betts et al., 2005, Yazdani et al., 2015). The significantly raised SSI in the F^- patient group, relative to the other epilepsy groups, could not be explained by differences in age or IQ (there was no difference in ACE scores between the epilepsy groups). And while we cannot fully discount a confounding effect of concurrent depression, this

condition is not known to be differentially associated with the presence, or absence, of generalised seizures in patients with focal epilepsy.

One of the speculations was that the behavioural consequence of surround suppression might be more likely to be observed in generalised compared to focal epilepsy. However, this result provides evidence that the visual psychophysical tests might also be useful in focal epilepsy. It can potentially be useful to predict who might have generalised seizures when at first the patient is presented with focal epilepsy, a fact that is critical for determining the risk of death in SUDEP (Sudden Unexplained Death in Epilepsy). In addition, this might explain why the start of a focal seizure could lead to recruiting the whole neuronal network in patients with generalised seizures. Perhaps this is suggestive of the effectiveness of inhibitory restraint in this group of patients (manifest as a higher suppression index). It is possible to speculate that the ability to increase the level of inhibition in respond to a seizure focus, protects these patients from seizure spread. But, other groups cannot increase their inhibitory restraint above controls' suppression level, and that is why they have generalised seizures. This might potentially suggest that an increased suppression index could be a sign of a lower risk of SUDEP compared to other patients with epilepsy.

Here we showed that patients with focal seizures without GTCS have distinctive surround inhibition compared to other patients groups (Figure 4.25).

There are different possible confounders between group of focal seizures and patients with generalised seizures, for example mesial temporal sclerosis often causes focal seizures, frontal lobe epilepsies often only cause focal seizures, and in patients with post traumatic, post stroke or tumour the incidence of GTCS is increased. Figure 4.25 demonstrates that those patients who have only focal seizures, have larger duration thresholds in the large high contrast. They have larger error-bars and more elevated duration thresholds of small high contrast compared to the other two groups. This raises the possibility of an inherent problem in this patients group due to factors other than motion discrimination. It is clear that the results of this group might be less reliable compared to other groups. The question that needs to be further studied is that are these patients have attentional difficulties?

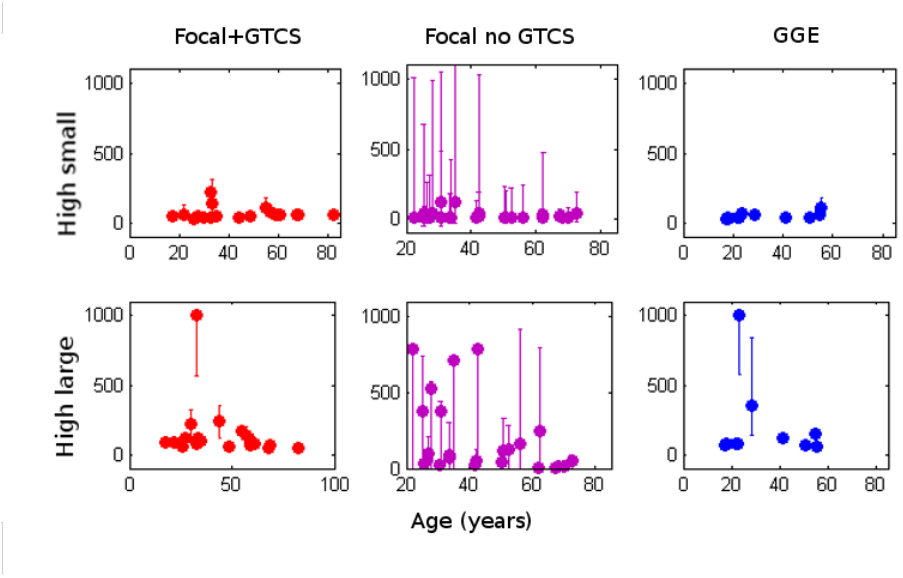


Figure 4.25. Duration threshold of small high contrast (top row) and large high contrast for patients based on their seizure subtypes. Patients with focal no GTCS show high thresholds of the large high contrast stimuli.

There are parallels between our study and a previous study of patients with migraine, who also showed evidence of increased suppression in a closely related perceptual task measuring contrast perception (Battista et al., 2011). The

intriguing possibility is that in these patients with focal (non-generalising) epilepsy, the pathological activity is kept focussed by an enhanced inhibitory restraint. Furthermore, it may therefore be possible to assess the quality of this restraint in regions of the cortex far removed from the focal pathology, as we do here with an assay of visual cortical function that appears to have relevance to foci elsewhere in the cortex. This presents an interesting question concerning whether the enhanced surround inhibition is independent of the epilepsy, or has arisen in reaction to the pathology, which will be addressed in future studies, requiring longitudinal, repeated testing of patients from the time of diagnosis. Whilst we have shown these differences between patients and controls, one major aim of this project was to see whether psychophysical tests could be a useful tool to predict seizures. For this to be the case we needed to see whether these once off changes persisted and indeed altered in the run up to a seizure. Hence the next set of experiments in the next chapter presents longitudinal data, from patients who were tested repeatedly over periods of days to weeks.

Chapter 5 Longitudinal study

5.1 Introduction

The occurrence of seizures is not uniformly distributed in time. They can occur as single seizures, or clusters, and it is this inherent unpredictability that causes a lot of risks such as higher chances of injury or psychological problems for patients. All of these associated risks with seizures decrease the overall quality of life in patients with epilepsy (Momeni et al., 2015, Ryan et al., 2015, Vickrey et al., 1994, Fisher et al., 2000). Therefore, there has been a great deal of interest in finding ways of predicting seizures (Cook et al., 2013) to give patients a better chance of avoiding injury, and the possibility of tailoring their medication to the current seizure risk.

Seizure prediction mainly consists of differentiating between preictal (time before a seizure) and interictal (time between seizures) signals in the brain. A lot of studies have shown that there are changes in the brain prior to seizures (Schwartz et al., 2011) and have concluded cortical hyperexcitability as a pre sign of the onset of clusters of seizures (Cook et al., 2013, Wright et al., 2006, Badawy et al., 2009). A functional MRI (fMRI) study done by Zhao et al. (2007) demonstrated focal increases in perfusion and decreases in hemoglobin oxygenation prior to seizure generation in one patient with epilepsy. In another fMRI study in three patients with intractable focal epilepsy highly significant, focal BOLD (Blood Oxygen Level Dependent) signal changes were observed prior to onset of seizures. These changes support the existence of a pre ictal state, however the changes were contralateral to the presumed seizure focus based on the symptoms in two of the patients (Federico et al., 2005). Other studies have shown evidence of changes between preictal and during interictal events (Perucca et al., 2014, Mormann et al., 2005). A number of studies suggested that

power spectral density of the EEG of patients with epilepsy is different before and during seizures (Bandarabadi et al., 2015, Park et al., 2011). Power spectral density has been used to design programmable devices to detect seizure activity and therefore send an electrical stimulation to stop the seizure activity. However, there have been a lot of problems with these studies, such as high number of false alarms and low sensitivity of seizure detection. Another significant problem with this method is heterogeneity of epileptic pathologies and that preictal and interictal events vary largely between patient to patient and even with a single patient these patterns could be different from a seizure to another (Zhang and Parhi, 2015). The most salient problem is that patients either need to have implanted devices or be connected to an EEG system, making it complicated for long-term home use.

In the previous chapter, I showed that people with different frequency of epilepsy syndromes appear to have differences in their measured suppression indices. We hypothesized therefore that these tests may also be used to follow these fluctuations in inhibition-excitation balance. If visual psychophysics are a means of indirectly measuring cortical inhibition, then using them might work as a way of monitoring and possibly an alternative tool to predict patients' seizures. This is what I test in this chapter; the performance of a number of patients with epilepsy were assessed in a longitudinal method to investigate whether there are changes in the inhibition in the run up to a seizure. Their performance were tested repeatedly over periods of days to weeks to observe their suppression indices variability over that period of time corresponding to their seizures in order to detect these extreme rare events (seizures).

5.2 Recruitment of subjects

Four healthy control participants were recruited for longitudinal test (3 male; mean age: 35.8; age range: 26.3-46.4). One control participant only took part in the motion discrimination task and 3 completed both the motion discrimination and contrast detection tasks.

Twenty patients with epilepsy were recruited for this longitudinal study, but four were unable to run the tests unaided, and so were excluded from further analysis (Table 5.1). Twelve patients were recruited from the video telemetry department of Royal Victoria Infirmary (RVI), 2 from a local epilepsy support group, and 6 from epilepsy clinics of RVI. Data of seven patients for the motion discrimination and 6 for the contrast detection tasks are presented as boxplots with respect to their timing of seizures. The rest of patients' suppression indices are shown in boxplots according to the time of their tests.

Table 5.1. Description of type of epilepsy in the longitudinal patients

Type of epilepsy-Aetiology	Number of longitudinal patients
Focal -unknown	9
Focal -structural-metabolic	6
Generalized -genetic	1

5.3 Experimental protocol

Tests were done on Samsung and Acer computer tablets (Table 2.1). Similar protocols that were explained in chapter 2 were followed for both the motion discrimination and the contrast detection tasks. Those who were recruited from the video telemetry department completed the tests in their hospital rooms; others took computer tablets to their homes. Before starting data collection all the patients were seen by the experimenter and had a chance to practice and

get familiarised with the equipment. Patients were told to repeat the tests at least 2 times per day, and as soon as possible after a seizure. Patients continued their medication while they were doing the tests.

The z-score of surround suppression indices for the motion discrimination and the contrast detection tasks were calculated using Equation 2.4, and based on the known time for a seizure, before and after points of that seizure were extracted.

These numbers were then plotted in boxplots as bee swarm plots (plot spread points) using MatLab to present the spread of data points, outliers and the median in each group.

5.4 Results

5.4.1 Controls showed surround suppression fluctuations during different times of a day or week

Results of surround suppression index of four controls during 4-5 continuous days are shown in Figure 5.1 and Figure 5.2. The upper panel in each figure respresents data collected from the motion discrimination task (Motion SI), and the bottom panel data from the contrast detection task (Contrast SI). Participants did the tests following each other, so each data point from upper and bottom panel were corresponding to one single point of time and one single run. Red data points are corresponding to the tests done before 12 in the morning and blue data points to those after 12 pm. Dotted vertical lines show the start and end of each day. If data points are not shown in any of the panels, it means that participant did not complete the test on that time of the day.

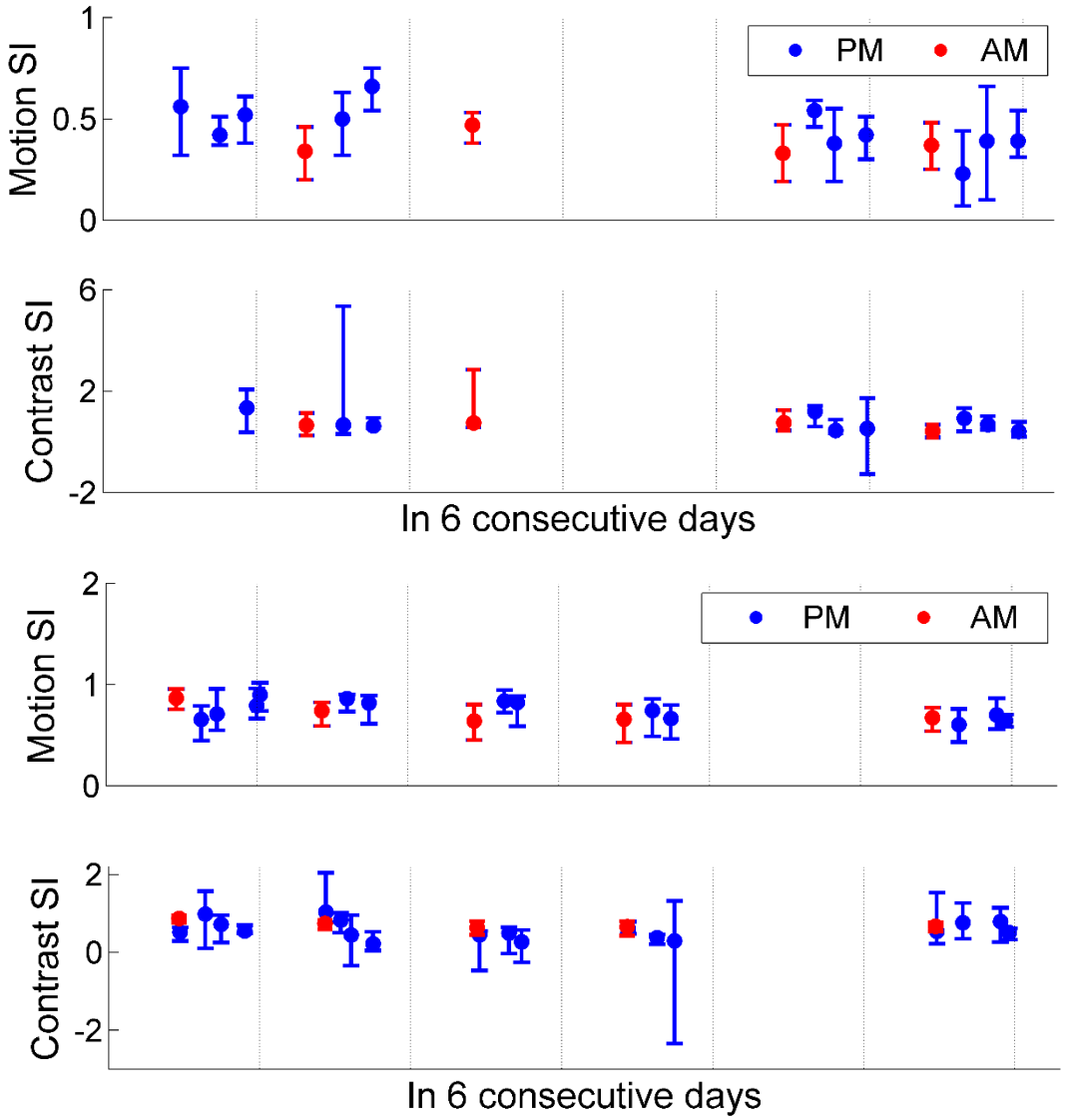


Figure 5.1. Longitudinal results of two control participants for motion discrimination task (Motion SI) and contrast detection task (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Error bars represent 95% confidence intervals.

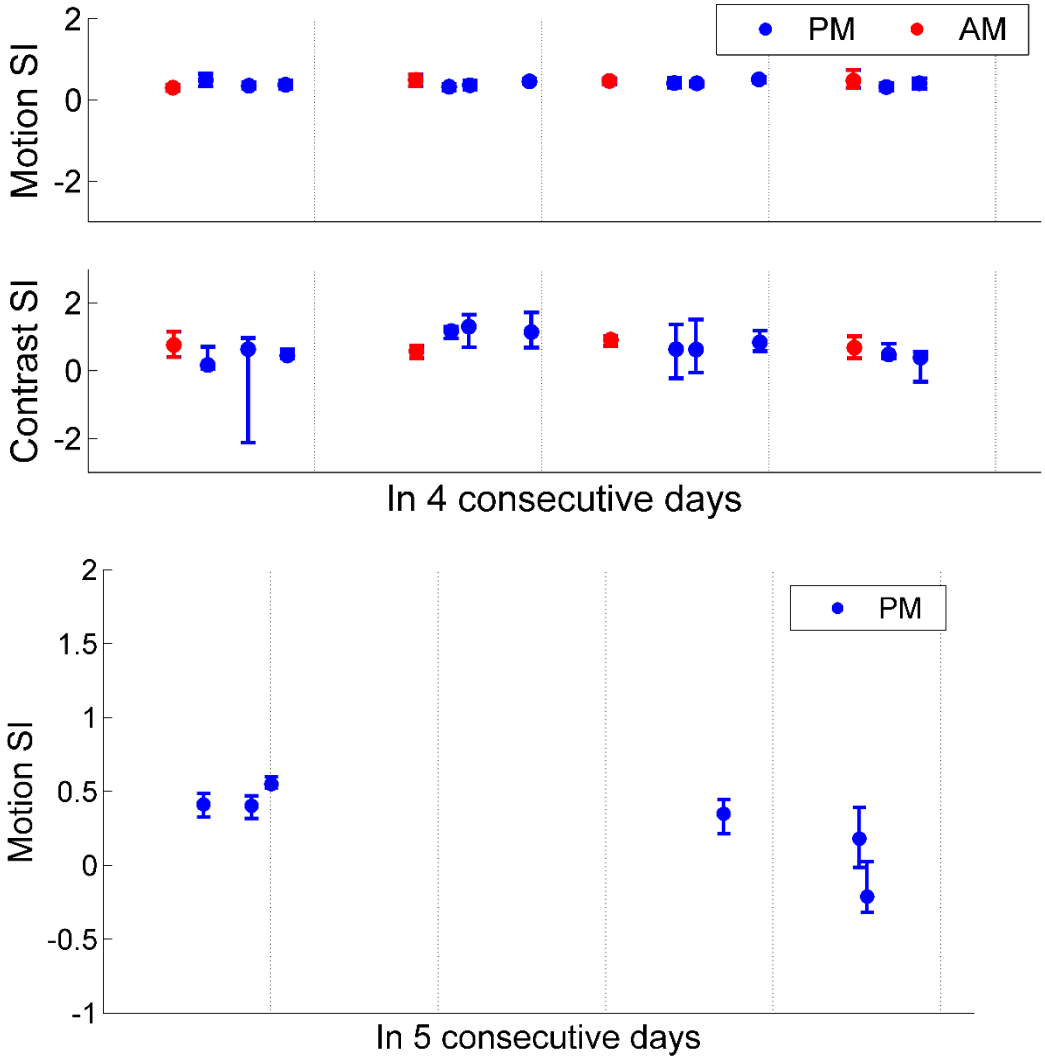


Figure 5.2. Longitudinal results of two more longitudinal control participants: top figure representing results of one control for the motion discrimination task (Motion SI) and contrast detection task (Contrast SI) and Bottom figure representing the motion discrimination task. This control did not perform the contrast detection task. Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Error bars represent 95% confidence intervals.

5.4.2 There is no indication of a link between circadian rhythm and fluctuations in the suppression indices

There is evidence suggesting that circadian changes might have interactions with epilepsy. The circadian rhythm is the system that makes organisms to be able to adapt to their environment with a cycle period of 24 hour. The primary circadian clock in mammalian is located in the cells of suprachiasmatic nuclei (SCN) situated in the anterior hypothalamus (Quigg, 2000). The circadian system is modulated by the external solar light and there are some evidence showing a link between seizures and their occurrence at nights in some types of epilepsy (Scheffer et al., 1995, Hofstra and de Weerd, 2009, Pung and Schmitz, 2006). Epilepsy and sleep have been studied greatly. For example, non-REM stage of sleep can increase the chance of partial seizures (Bazil and Walczak, 1997). We could not run the visual psychophysical tests during the subjects' sleep, however they were advised to run the tests between 2 to 3 times per day. Therefore, boxplots of controls (Figure 5.3) and patients (Figure 5.4) were plotted in order to find any difference between fluctuations of suppression indices and time of the day.

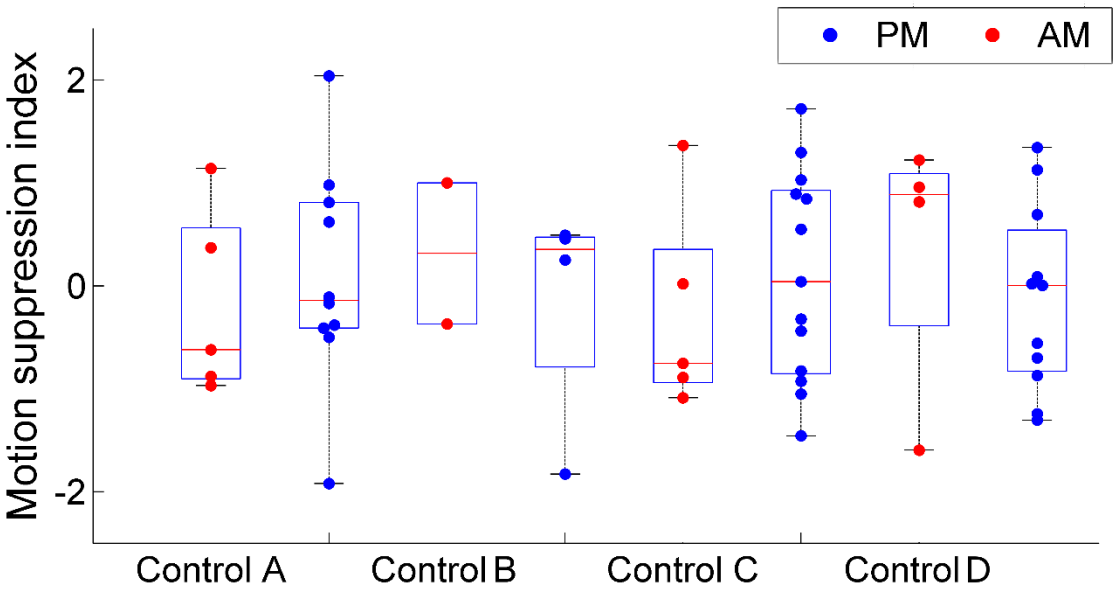


Figure 5.3. Bee swarm boxplots of controls showing their motion suppression index before noon (in red AM) and after noon (in blue PM).

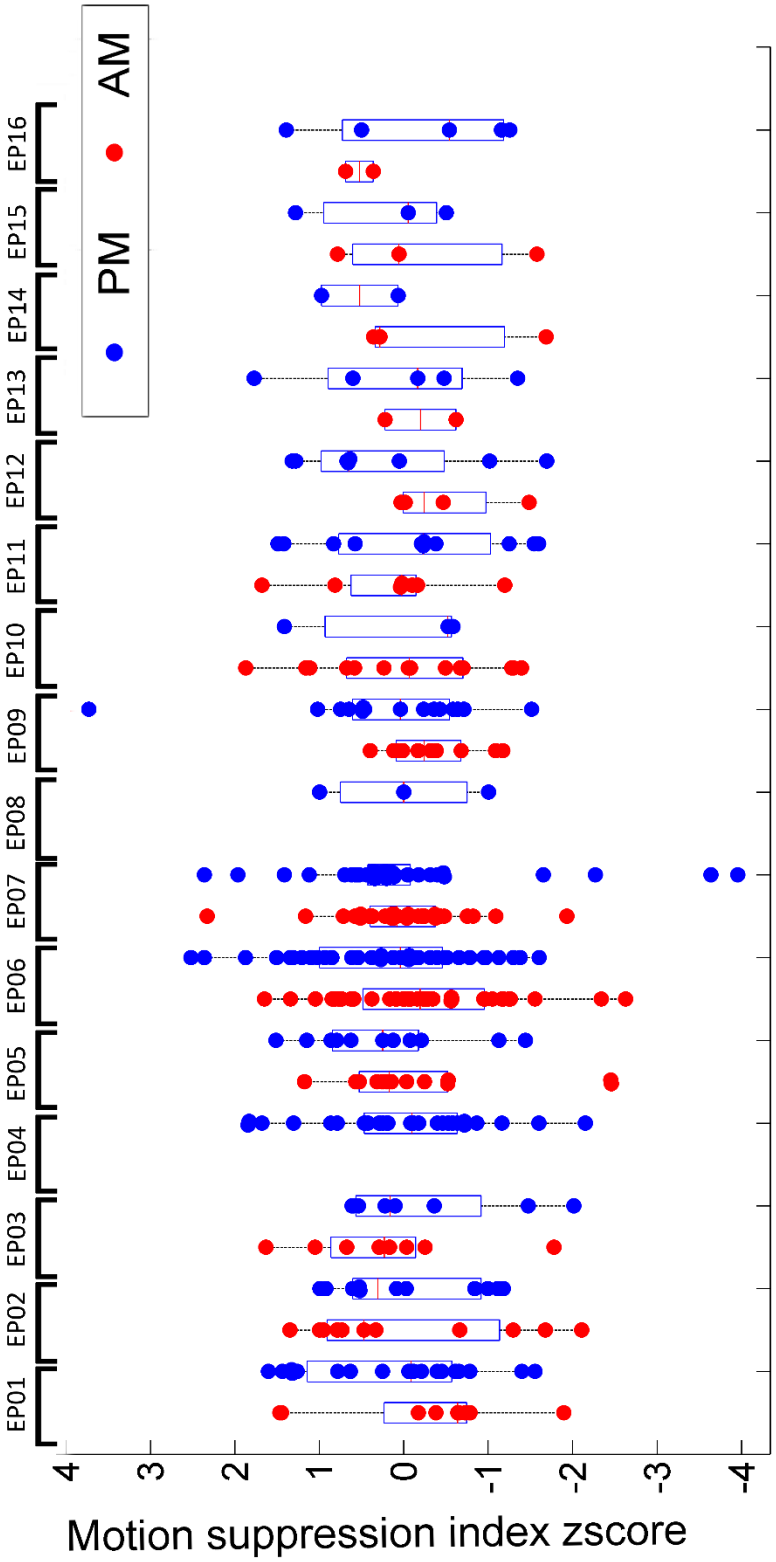


Figure 5.4. Bee swarm boxplots of 16 patients showing their motion suppression index z-score before noon (in red AM) and after noon (in blue PM). Every two boxplots belongs to one patient and the lack of a boxplot for any patient indicates that patient did not perform the motion discrimination task in that time period of that day.

Figure 5.5 captures a plot of boxplots comparing all the patients and controls based on the time of performing the test (before noon (AM) and after noon (PM)).

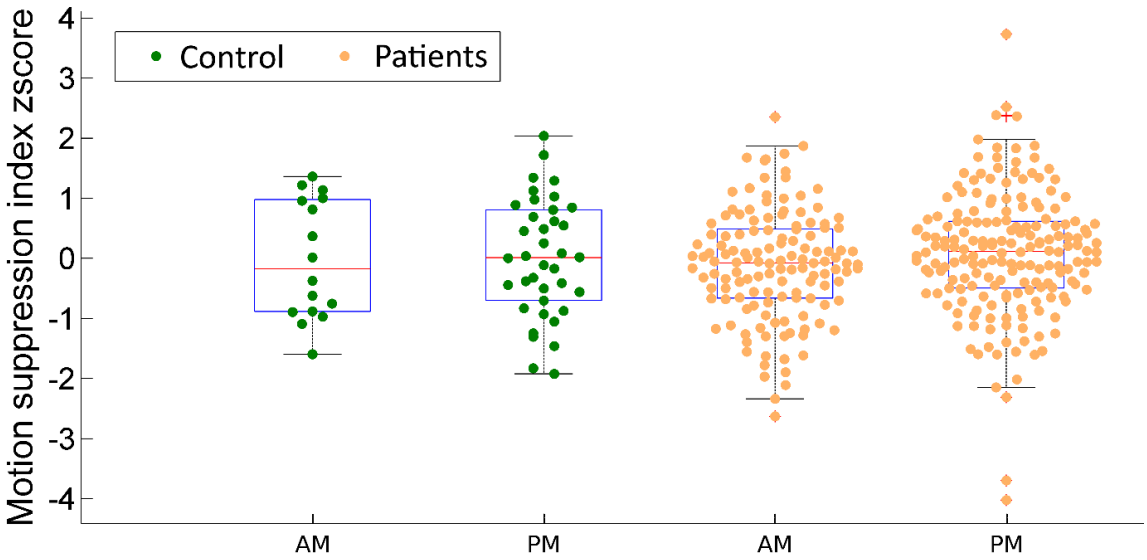


Figure 5.5. Bee swarm boxplots of all sixteen patients (in orange) and four controls (in green) with their motion suppression index z-scores before noon (AM) and after noon (PM).

5.4.3 Patients and controls showed non-significant difference in variations in suppression indices

When considering the differences in the two groups with repeated measurements, it is important to study both the between subject and within-subject variations. To do so, first suppression indices of controls and patients were normalised to their mean and then were plotted in Figure 5.6 for the motion discrimination task and in Figure 5.7 for the contrast detection task. Similarly, Figure 5.8 and Figure 5.9 demonstrate normalised suppression indices for all the individual participants. Nine patients did not have any seizures during the course of the test. The number of seizures out of the overall duration of the test is shown on the top of Figure 5.8 and Figure 5.9. For example 3(25) means

that this patient had 3 seizures in 25 days of running the test. And where there is no number it simply means that this patient did not have any seizures.

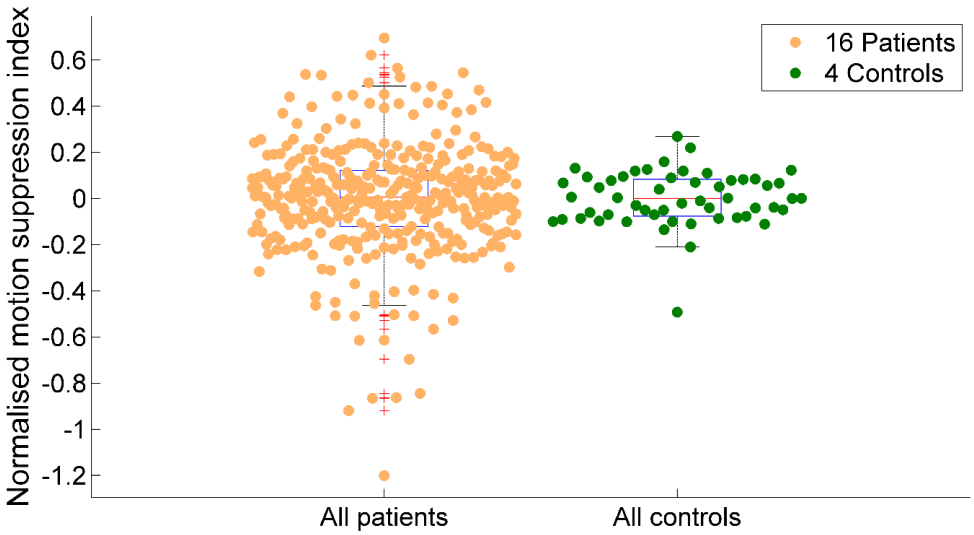


Figure 5.6. Bee swarm plots of pooled data of normalised suppression index for all the patients (in orange) and controls (in green) for the motion discrimination task.

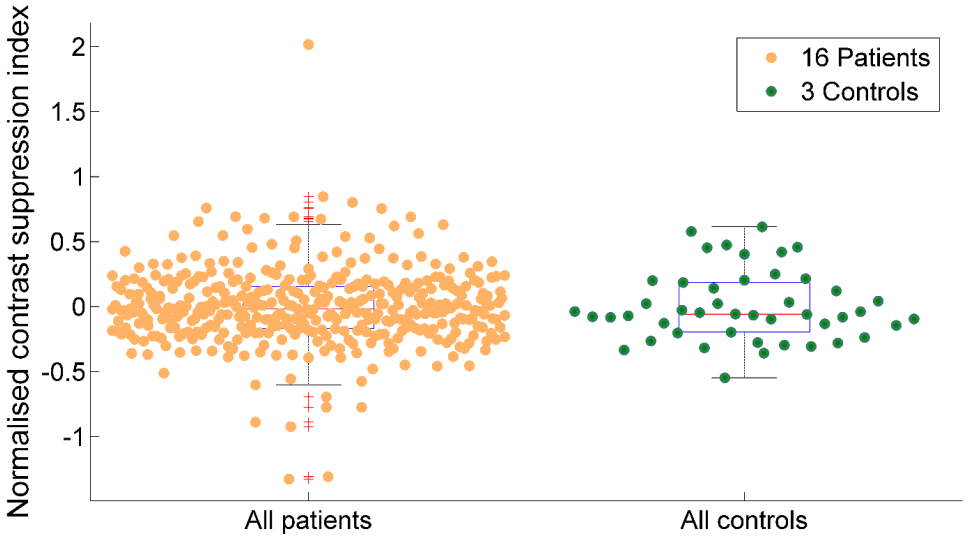


Figure 5.7. Bee swarm plots of pooled data of normalised suppression index for all the patients (in orange) and controls (in green) for the contrast detection task.

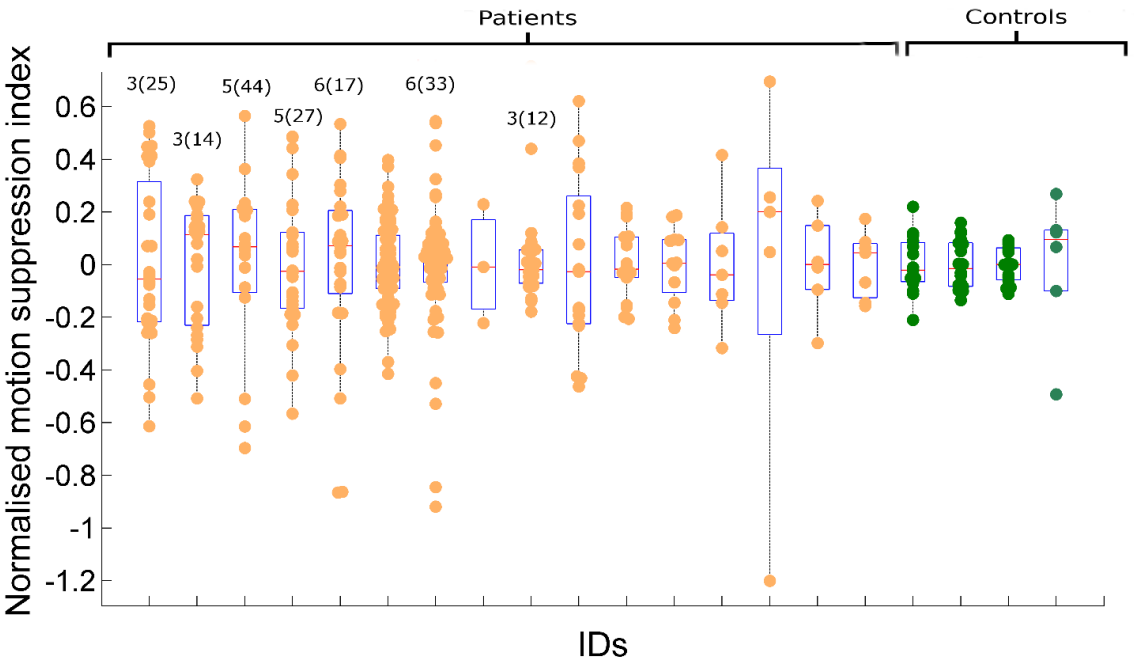


Figure 5.8. Bee swarm plots of pooled data of sixteen patients and four controls in the motion discrimination task. The number of seizures and the duration in days for which the patients repeated the tests are shown in the figure. Thoese patients who are not enumerate did not have any seizures.

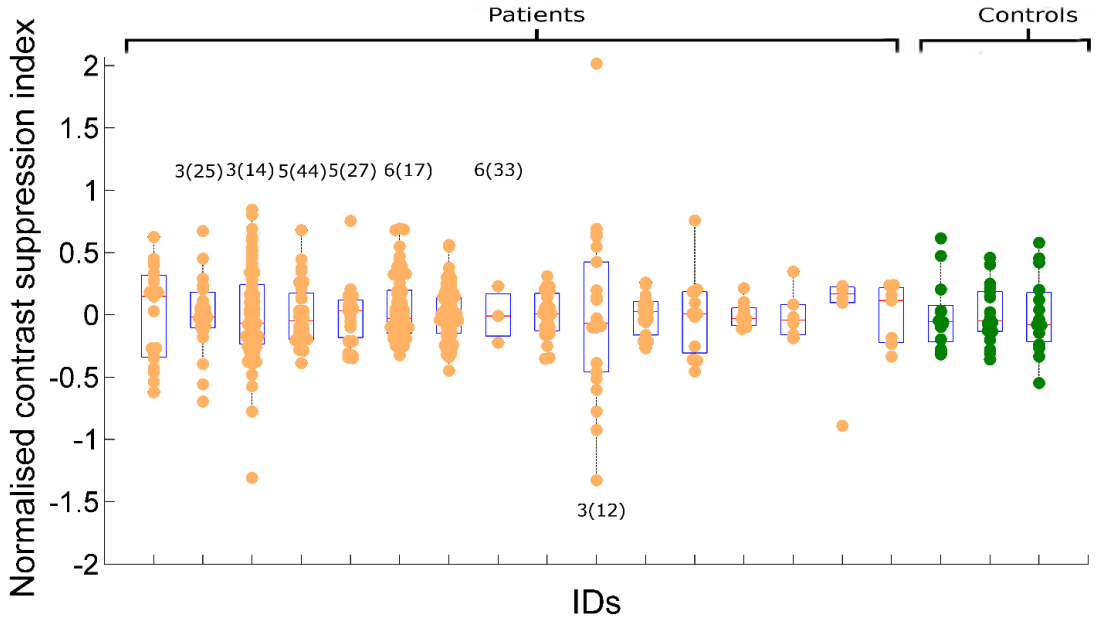


Figure 5.9. Bee swarm plots of pooled data of sixteen patients and three control subjects in the contrast detection task. One control did not perform the contrast detection task. The number of seizures and the duration in days for which the patients repeated the tests are shown in the figure. Those patients who are not enumerated did not have any seizures.

Figure 5.8 and Figure 5.9 show participants variability in their surround suppressions as boxplots. However, it is necessary to calculate the variability in the suppression indices in both between subjects and within-subjects. The estimate of the variability in the patients and control groups are shown in Table 5.2.

Table 5.2. Estimated standard deviations of between and within subjects

	PATIENTS (n=16)		CONTROLS	
	Motion suppression index	Contrast suppression index	Motion suppression index (n=4)	Contrast suppression index (n=3)
Between subjects error	0.367	0.159	0.195	0.080
Mean within-subject error	0.258	0.283	0.135	0.276

A non-parametric Levene's test showed equality of between-subject variances in both controls and patients (Motion suppression index: p=0.46; Contrast suppression index: p=0.06; with data being the mean suppression index obtained across repeated measurements for each person). To compare the within-subject error, we computed the SD of the repeated measurements for each person, so ending up with a set of within-subject SDs for patients and for controls. A non-parametric Mann-Whitney U test indicated that these did not differ significantly (Motion suppression index: Mann-Whitney U=11, p=0.05 (two-tailed); Contrast suppression index: Mann-Whitney U=20, p=0.7).

We were also interested to find whether there is any relationship between fluctuations in suppression indices and patients' time of seizures, because for the visual psychophysics to be a useful predictor of seizures it must provide us with a detectable change leading up to a seizure. Therefore, patients' data were separated into four individual groups with respect to their seizures over the time course of participation. These groups were data from "before a seizure", "after a seizure", "other" data points which were times when no seizure was reported, and "overall data points" which was the pooled collection of all data points. Since there were occasions that patients did not know the exact time of their seizures, or did not properly record them, three different timescales were considered: 24 hour, 12 hour, and 6 hour before and after a seizure.

Only seven patients had seizures during the time of participation in the longitudinal task. The following plots demonstrate data of seven individual patients for motion discrimination and contrast detection tasks as bee swarm and longitudinal plots.

Figure 5.10 demonstrates bee swarm figure of one of these patients with presumed temporal focal dyscognitive seizures on the motion discrimination task. There was a change of medication in the time course of participation in this patient, in which Perampanel was added to reduce the number of seizures (started with 6mg which was later increased to 8mg). After this point, some adverse behavioural changes were observed in the patient. There seems to be an elevated suppression index in both before and after seizure groups, however it is not clear whether this was due to medication or different underlying neuronal mechanisms. Student's t test (unpaired t-test) showed significant differences between before a seizure and other data points ($t=3.08$, $p=0.03$) and between after a seizure and all data points ($t=5.5$, $p<0.001$) in all conditions. This patient declined performing the tests after a few days of starting Perampanel,

and further correspondence was unsuccessful. Therefore, it was impossible to gather further data to increase the sample size and to capture more seizures in order to increase the data points in “before” and “after” a seizure groups. The fact is that most of the data points are in the “other” group and the result of the analysis could be distorted with some data points as outliers in the “other” group. As it is clear in further figures for the rest of patients, we did not find any significant difference between any of the groups.

Figure 5.10 to Figure 5.23 show bee swarm results of the rest of patients who did the longitudinal tests. Detailed description of each patient is included in corresponding figure legend. Note that y-axis in the bee swarm plot are the z-score representation. There was no significant difference between times of seizures and other data points in the other patients. Therefore, there was no sign of a consistent relationship between the times of seizures and suppression indices.

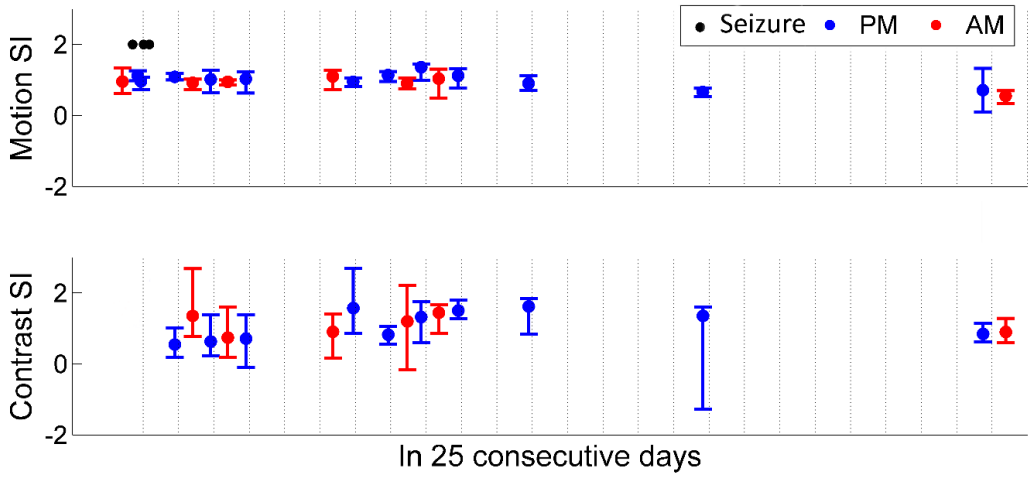


Figure 5.10. Longitudinal results of a patient (EP01) representing results of the motion discrimination task (Motion SI) and contrast detection task (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

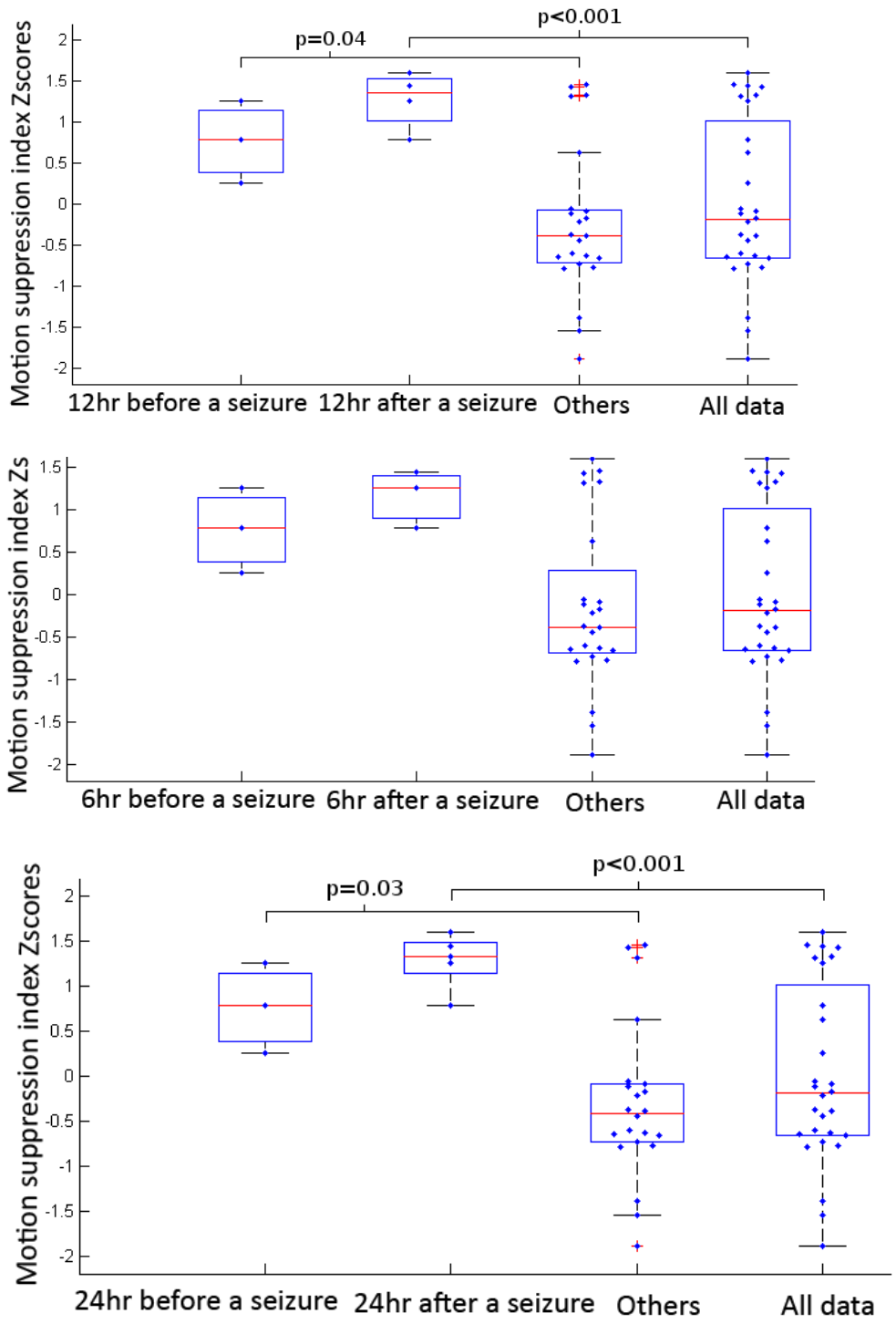


Figure 5.11. Bee swarm plots representing longitudinal results of a patient (EP01) in the motion discrimination task. Y-axis represents SSI Zscores .The duration of participation was 1 month, during which 3 seizures were reported. This patient was diagnosed with (presumed) temporal focal dyscognitive seizures with frequency of more than one per week. Medication was Levetiracetam and Pregabalin. Perampanel was added later after which, the patient showed severe behavioural changes.

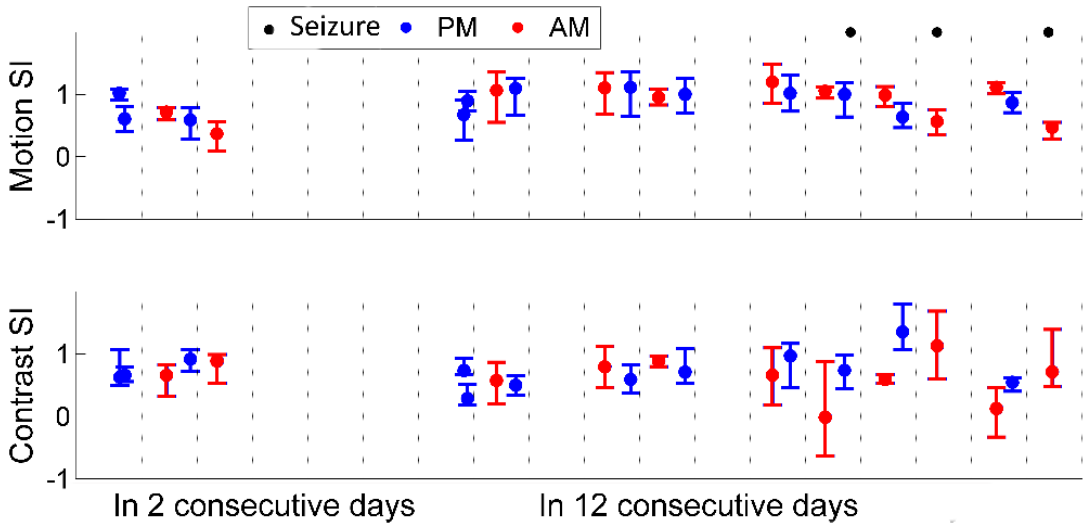


Figure 5.12. Longitudinal results of a patient (EP02) representing results of the motion discrimination (Motion SI) and contrast detection tasks (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. There were 4 weeks between the two set of data collection. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

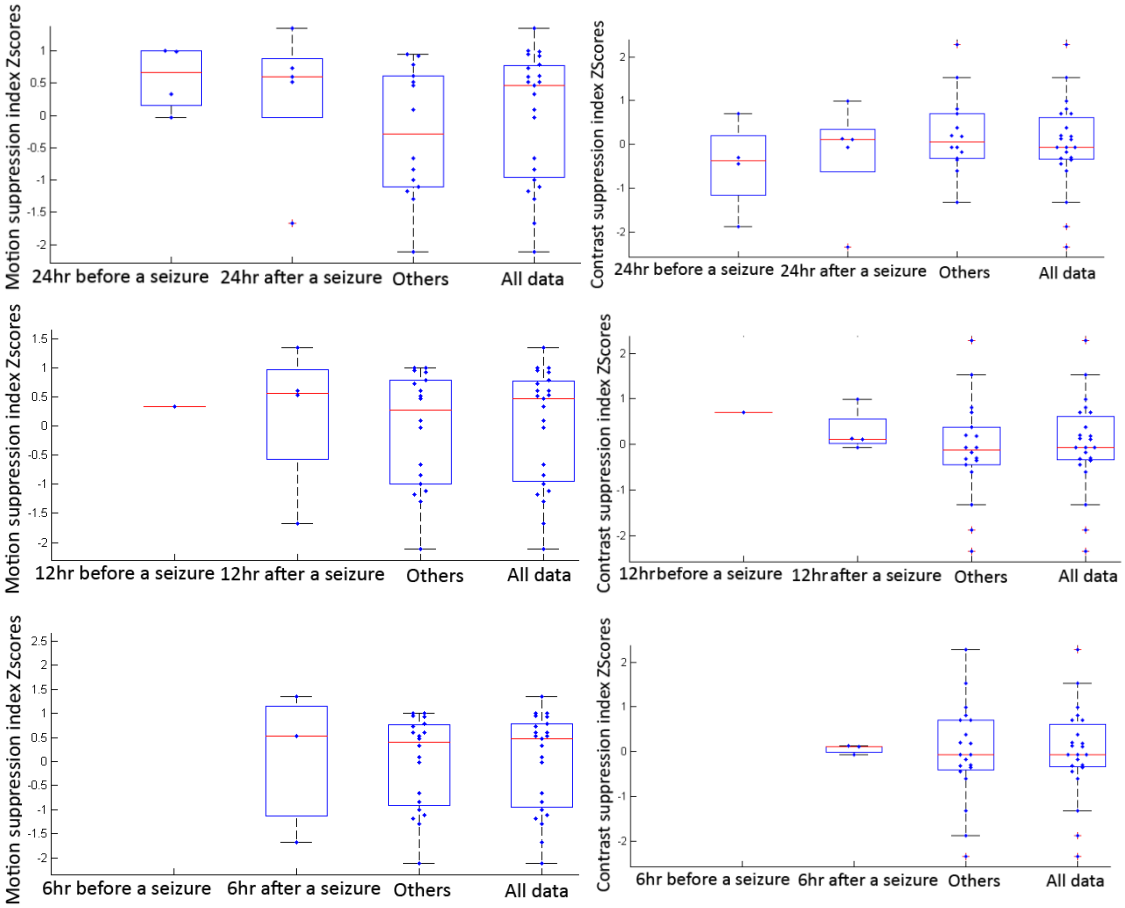


Figure 5.13. Bee swarm plots representing longitudinal results of a patient (EP02) in the motion discrimination (left panel) and contrast detection tasks (right panel). Y-axis represents SSI Zscores .The duration of participation was around 2 weeks, during which 3 seizures were reported. This patient was diagnosed with temporal focal dyscognitive seizures with frequency of more than one per week as clusters. The medication was Lamotrigine and Pregabalin.

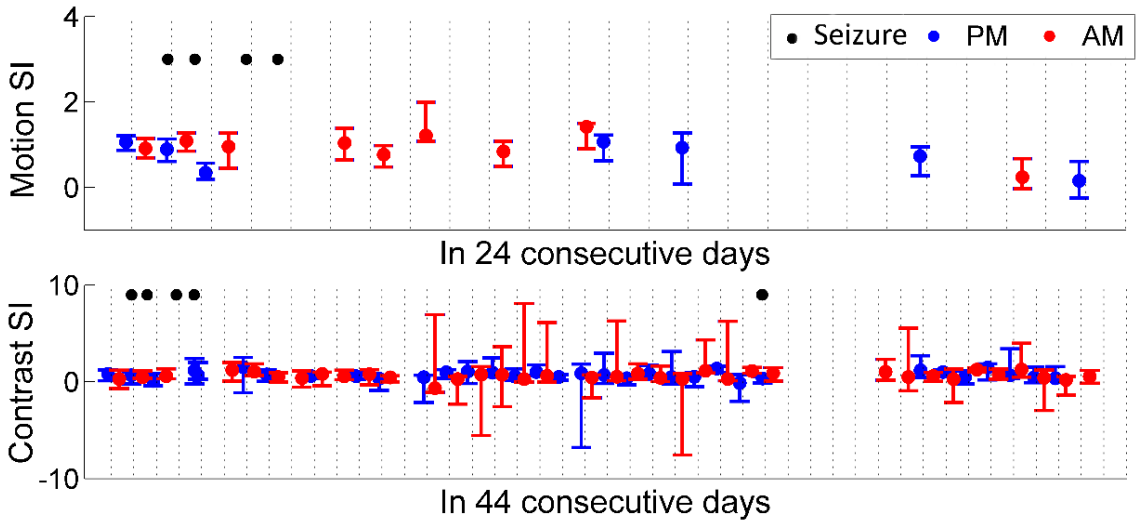


Figure 5.14. Longitudinal results of a patient (EP03) representing results of the motion discrimination (Motion SI) and contrast detection tasks (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Motion discrimination task data collection was shorter than the contrast detection task because the results of staircases were inconclusive. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

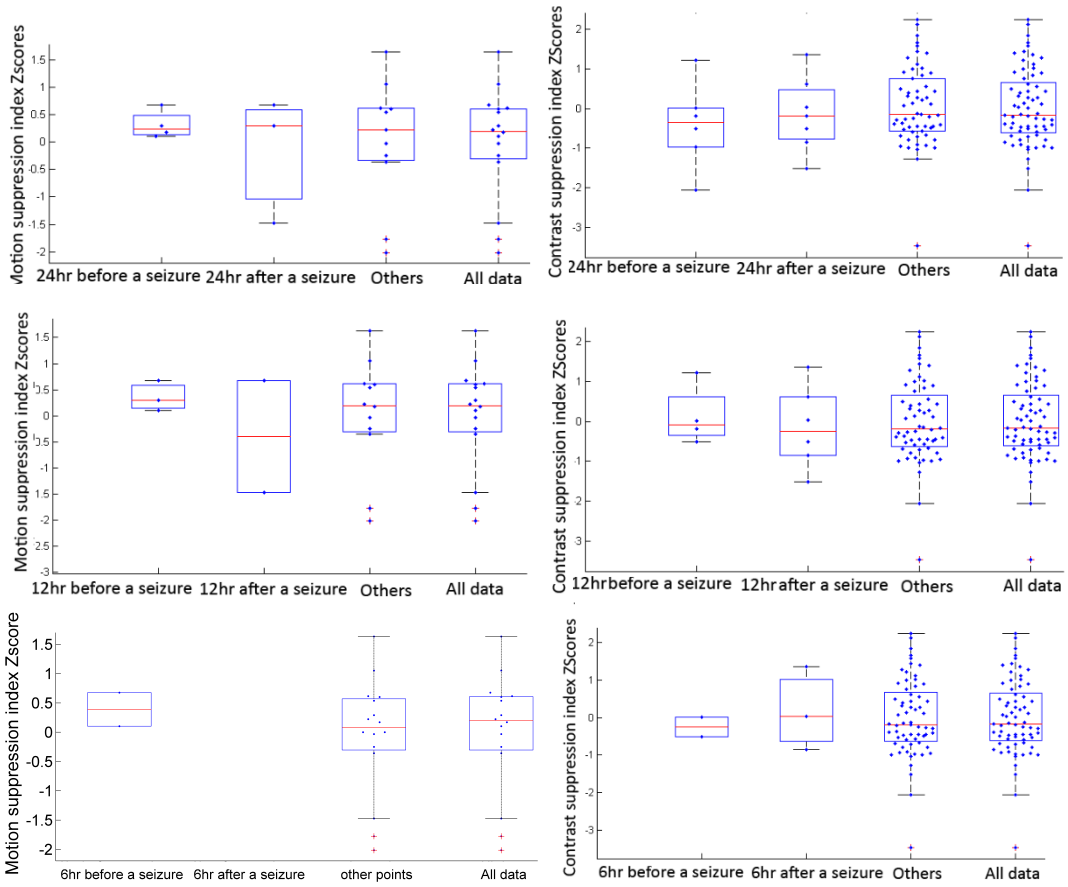


Figure 5.15. Bee swarm representing longitudinal results of a patient (EP03) in the motion discrimination (left panel) and contrast detection tasks (right panel). Y-axis represents SSI Zscores. Five seizures were reported during the time of participation. This patient was diagnosed with (presumed) fronto-temporal focal dyscognitive and absence seizures with frequency of more than one per week. The medication was Sodium Valproate and Lamotrigine.

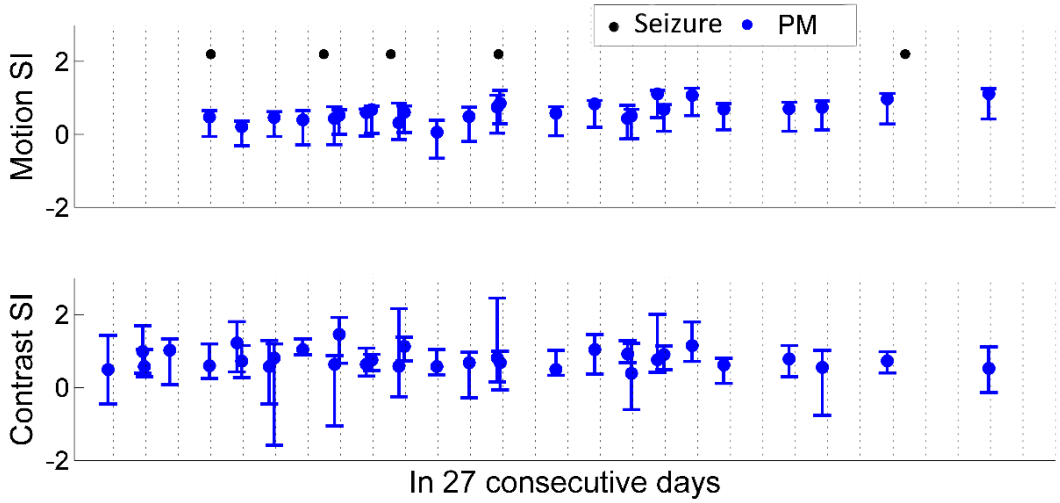


Figure 5.16. Longitudinal results of a patient (EP04) representing results of the motion discrimination task (Motion SI) and contrast detection task (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

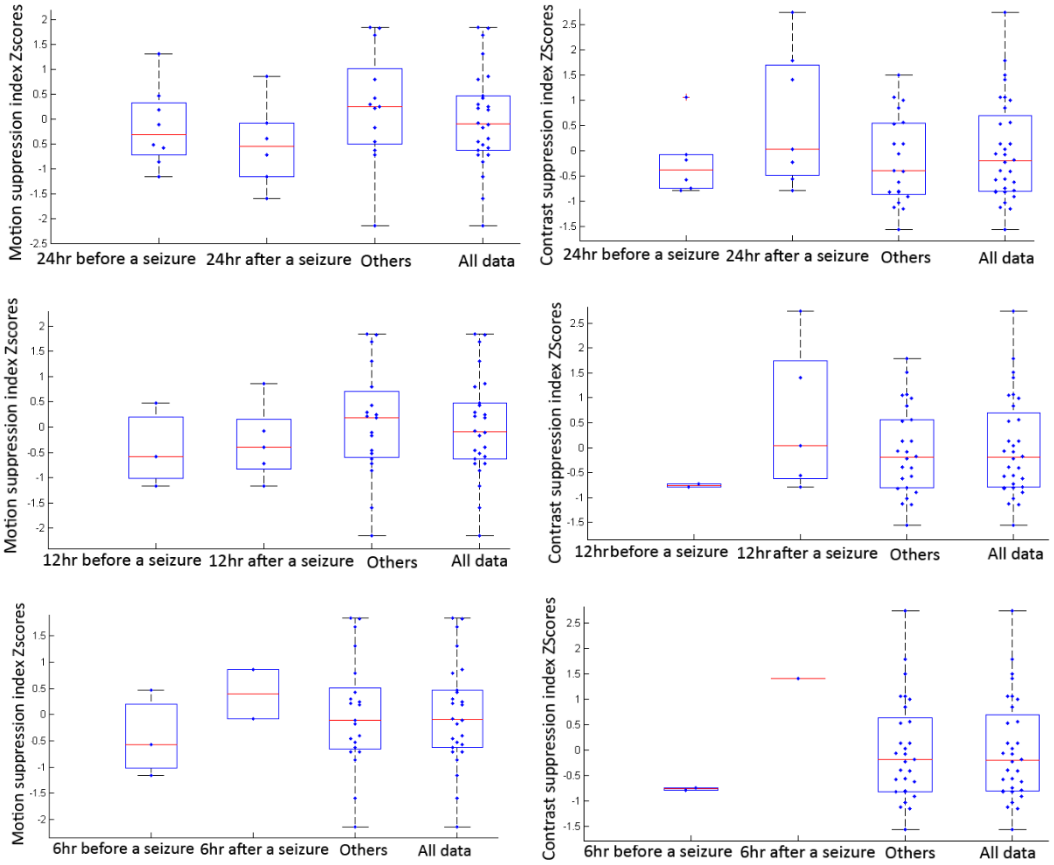


Figure 5.17. Bee swarm representing longitudinal results of a patient (EP04) in the motion discrimination (left panel) and contrast detection tasks (right panel). Y-axis represents SSI Zscores. The duration of participation was 27 days, during which 5 seizures were reported. This patient was diagnosed with frontal focal dyscognitive seizures with frequency of more than one per week. The medication was Sodium Valproate, Pregabalin, Eslicarbazepine, and Phenobarbitone.

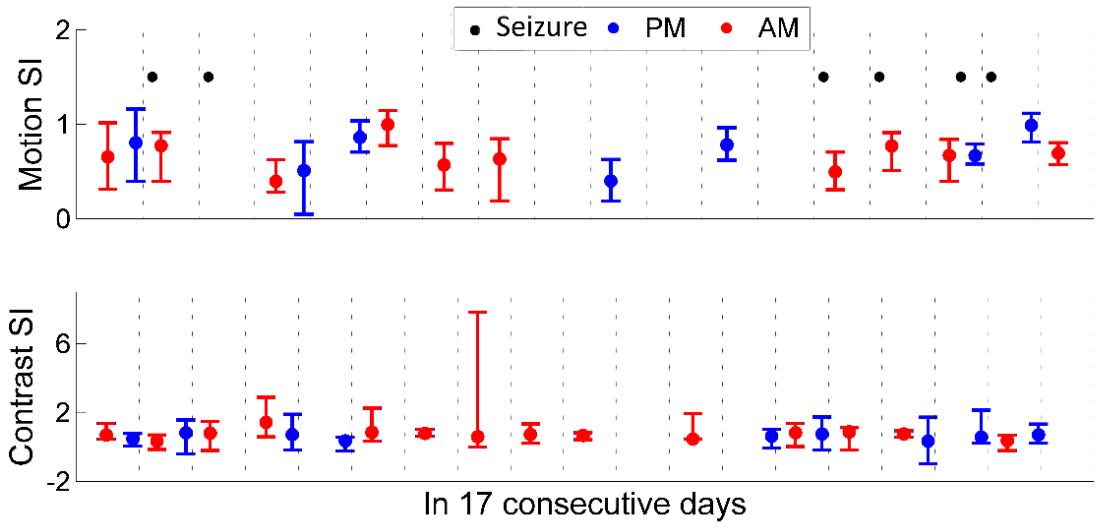


Figure 5.18. Longitudinal results of a patient (EP05) representing results of the motion discrimination (Motion SI) and contrast detection tasks (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

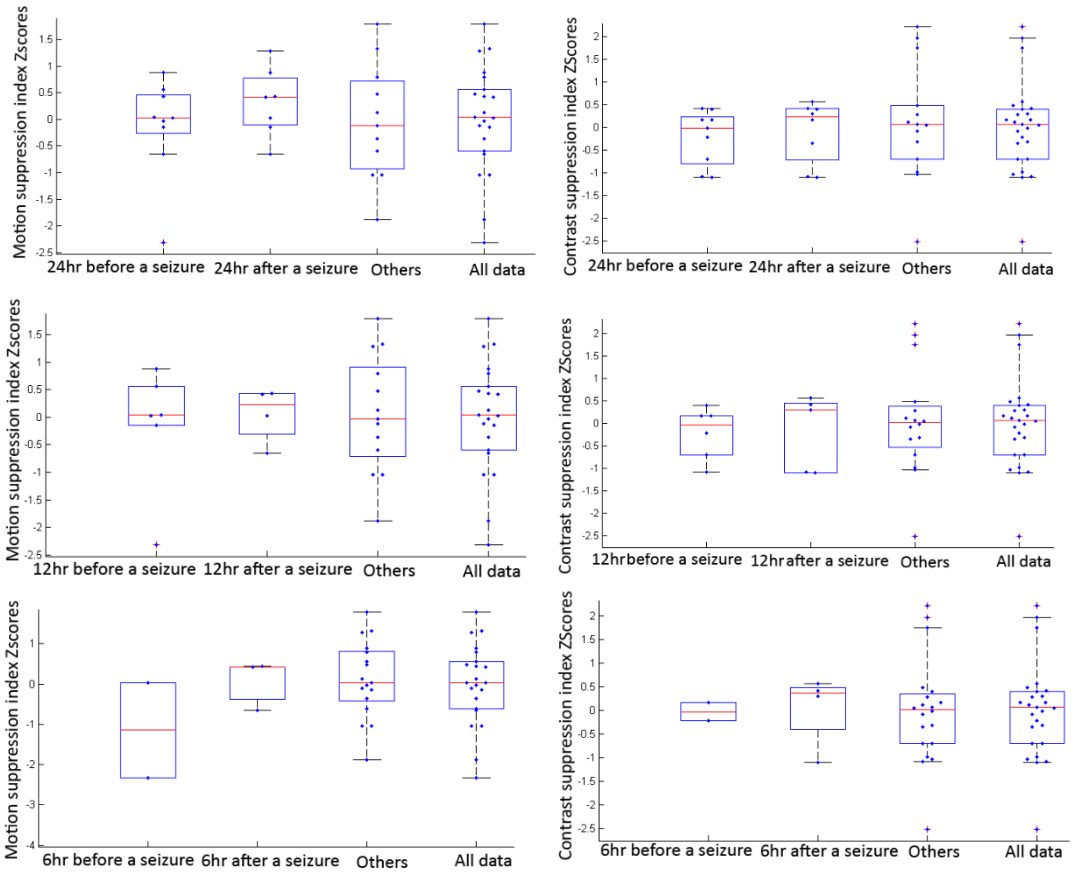


Figure 5.19. Bee swarm plots representing longitudinal results of a patient (EP05) in the motion discrimination (left panel) and contrast detection tasks (right panel). Y-axis represents SSI Zscores. The duration of participation was 17 days, during which 6 seizures were reported. This patient was diagnosed with nocturnal seizures initiated from temporal lobe with possible abnormality in left hippocampus. The frequency of seizures was more than one per week. The medication was Pregabalin, Levetiracetam, Tegretol, Phenytoin, and Clobazam.

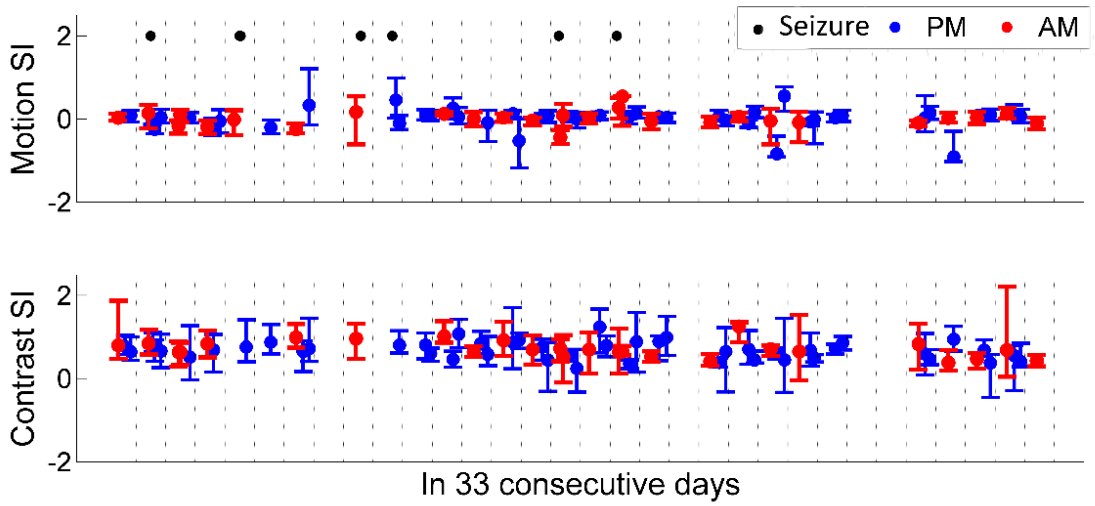


Figure 5.20. Longitudinal results of a patient (EP07) representing results of the motion discrimination (Motion SI) and contrast detection tasks (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

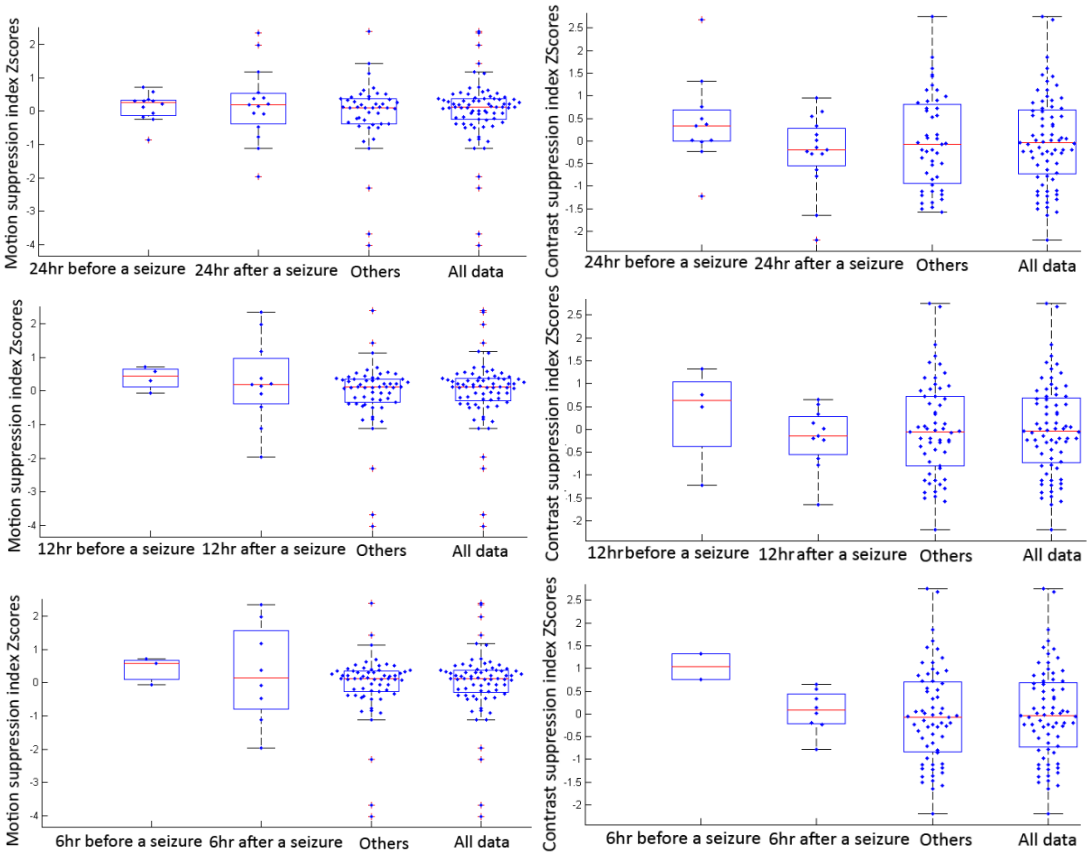


Figure 5.21. Bee swarm plots representing longitudinal results of a patient (EP07) on motion discrimination (left panel) and contrast detection tasks (right panel). Y-axis represents SSI Zscores. The duration of participation was 33 days, during which 6 seizures were reported. This patient was diagnosed with temporal lobe epilepsy with left mesial temporal sclerosis. The frequency of seizures was more than one per week. The medication was Clobazam, Epilim (sodium valproate), and Carbamazepine.

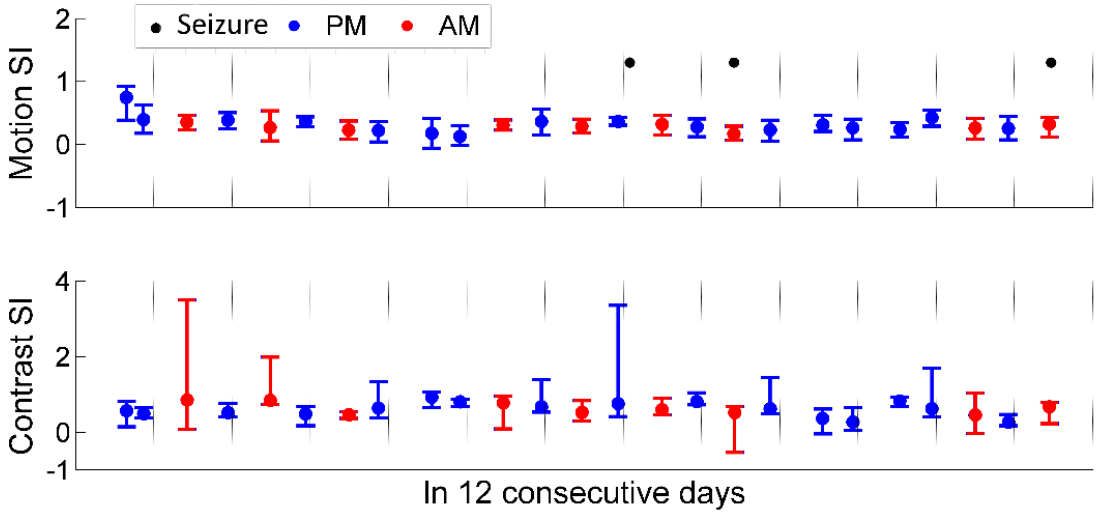


Figure 5.22. Longitudinal results of a patient (EP09) representing results of the motion discrimination (Motion SI) and contrast detection tasks (Contrast SI). Y axes represents suppression index and x axes the time of the day at which the test was performed. Dotted lines show the end of each day of data collection. Data collection was done in continuous days. Blue and red points show data collected in the afternoon and before noon, respectively. Black circles show the exact time of seizures. Error bars represent 95% confidence intervals.

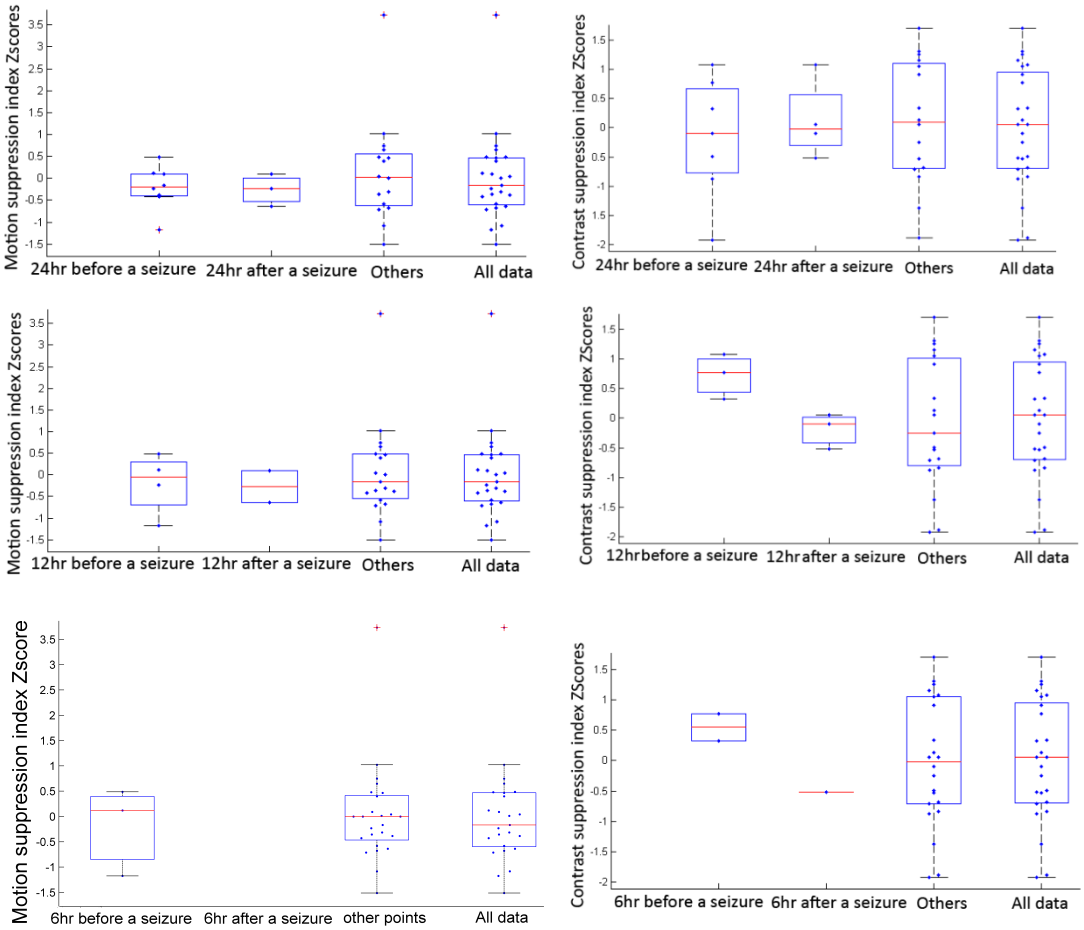


Figure 5.23. Bee swarm plots representing longitudinal results of a patient (EP09) on motion discrimination (left panel) and contrast detection tasks (right panel). Y-axis represents SSI Zscores. The duration of participation was 12 days, during which 3 seizures were reported. This patient was diagnosed with generalised tonic clonic epilepsy with complex partial seizures. The frequency of seizures was around 1 every two months. The medication was Lamotrigine and Topiramate.

Figure 5.24 shows bee swarm figures of data pooled from all the patients based on 24 hour, 12 hour and 6 hour before and after a seizure along with other data points. Statistical tests did not show any significant difference among the groups.

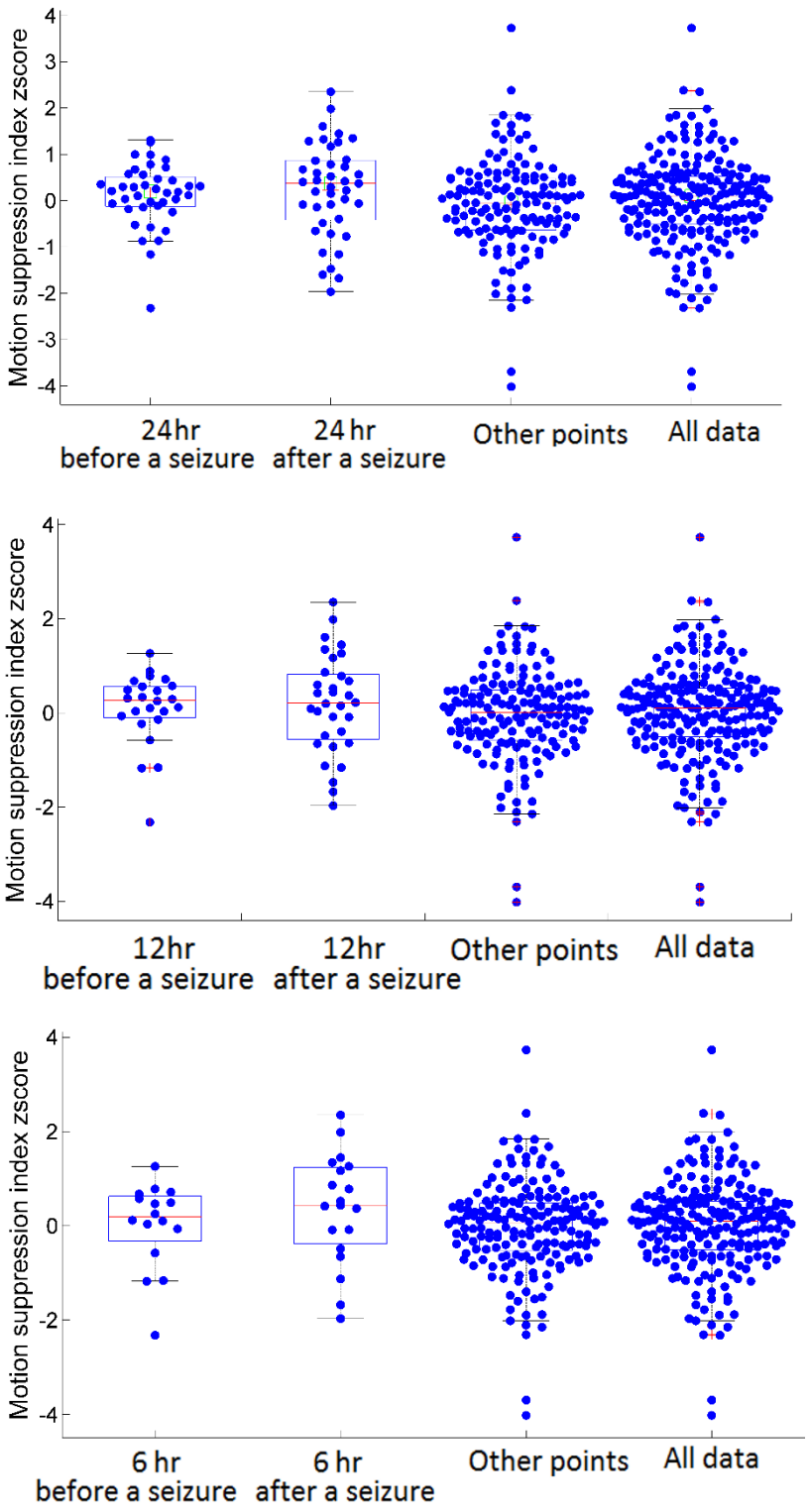


Figure 5.24. Bee swarm plots of all the patients pooled according to 24 hour, 12 hour and 6 hour before and after a seizure. Other points demonstrate those times that were not associated with a seizure. Note that y-axis is the z-score representation

Figure 5.25 shows boxplot figures of 24hr, 12hr and 6hr before a seizure for all the patients in the motion discrimination (top figure) and the contrast detection tasks (bottom figure). Statistical tests indicated no significant differences between the groups.

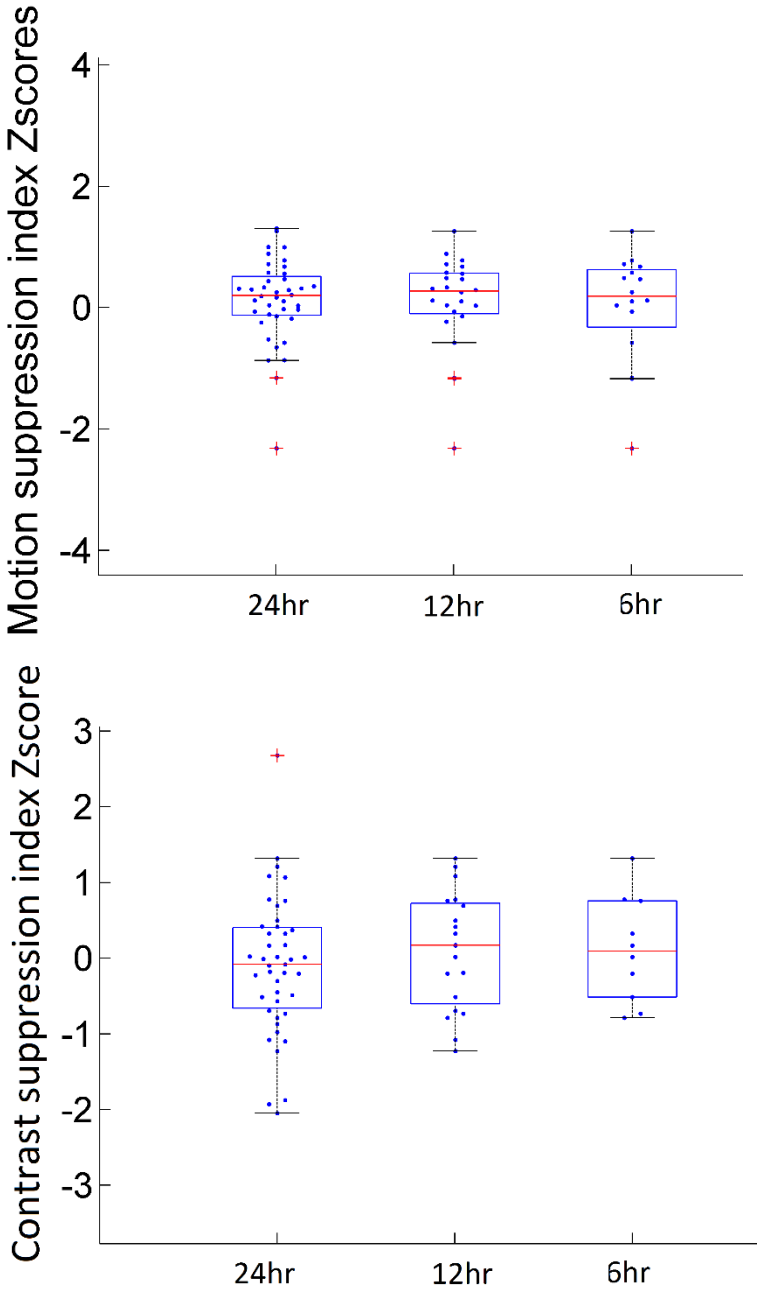


Figure 5.25. Bee swarm figures of the motion discrimination task (top) and the contrast detection task (bottom) for all the patients 24 hr, 12 hr and 6 hr before a seizure. Note that y-axis is the z-score representation.

5.5 Discussion

Longitudinal tests of the motion discrimination and contrast detection tasks were performed on 20 patients with epilepsy and 4 healthy controls. Only seven patients had seizures during the longitudinal test, and therefore data analysis of these seven patients were provided in details in this chapter. In chapter 4 we found a significant difference between patients and controls in the motion suppression indices measured at a single time point, and so in this chapter we investigated the possibility of a link between inhibitory fluctuations and occurrence of seizures in patients with epilepsy using visual psychophysical tests. We hypothesized that these fluctuations reflect an altered state of excitability and inhibitory forces in patients and could therefore be a used as an indication or warning for predicting a seizure. We speculated that patients with epilepsy will show variation in their suppression indices, and variations below a hypothetical threshold might suggest a relationship with timing of their seizures. Accordingly, controls would display no, or less, variation in the measured surround suppressions compared to patients (Figure 5.26 to Figure 5.28).

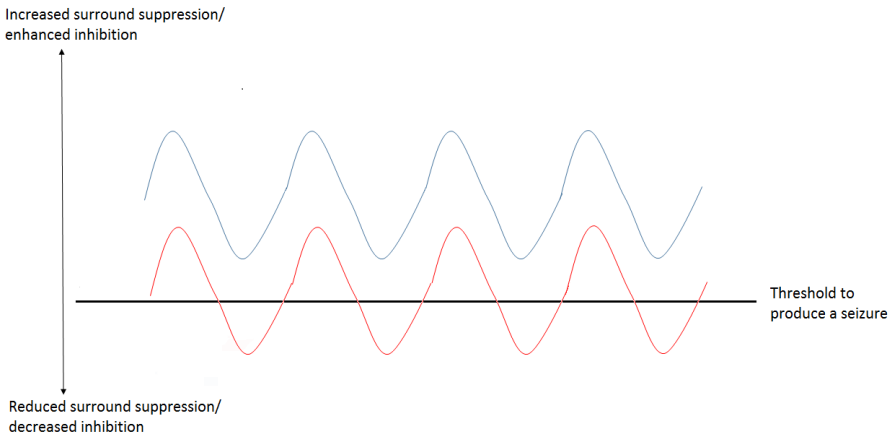


Figure 5.26. Examples of fluctuations in surround suppression in a control (in blue) and a patient (in red). Shift in the baseline or fluctuation can produce a seizure.

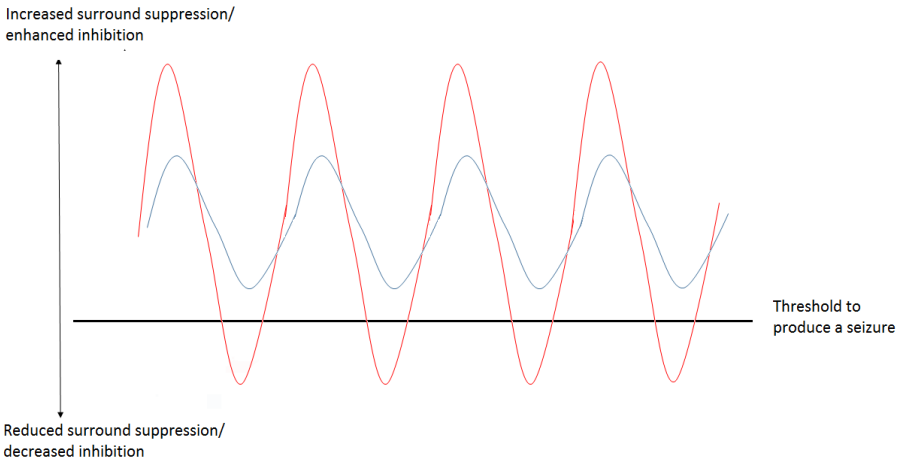


Figure 5.27. Examples of fluctuations in surround suppression in a control (in blue) and a patient (in red). Increase in the fluctuations in red might produce a seizure (here in red).

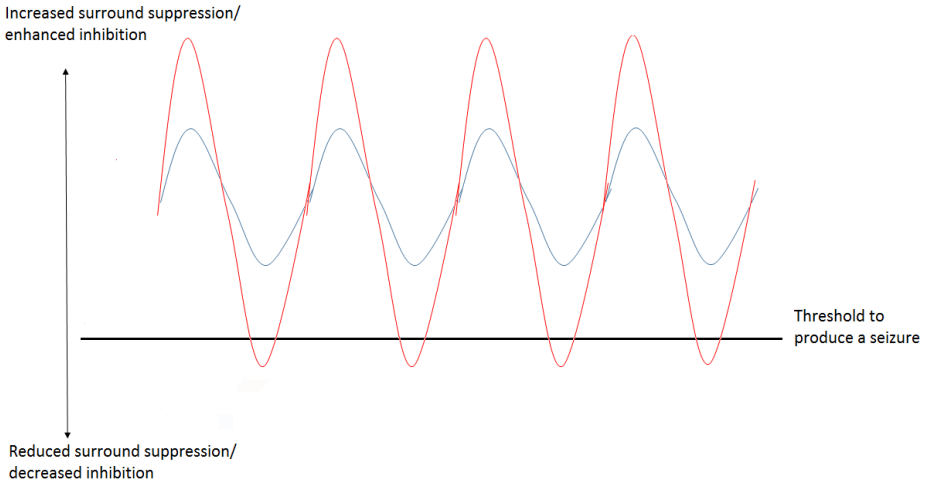


Figure 5.28. Examples of fluctuations in surround suppression in a control (in blue) and a patient (in red). Another example of occurrence of a seizure could be with shifted baseline along with increased fluctuations (here in red).

In order to obtain results, twenty patients agreed to perform the tests in over periods of 1 week to 2 months, repeating the tests at least twice a day. They were asked to continue doing the tests until they had more than two seizures. This was done to ensure having minimum 2 points of seizures to perform the assessment between seizures and non-seizures data points. Final assessment revealed that only 7 people with epilepsy had seizures during the course of participation and the remaining declined to perform the test, or could not use

the tablet computers (even after training). The experimenter had regular visits to patients' houses to ensure patients were following the correct protocol.

Results from these 7 patients are shown in Figure 5.10 to Figure 5.23. The outcome of these plots did not point to any significant relationship between the fluctuations and timing of seizures that was also consistent in all of the patients. Only one of the patients (EP01), shown in Figure 5.11, had significant difference in suppression indices among the groups of before, after, and other data points. Due to worsening of seizures, this patient was prescribed with Perampanel at the same time of performing the tests. Perampanel is an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist which reduces excitatory synaptic transmission. Although the frequency of seizures decreased dramatically, it resulted in distress and violent behaviour. Perampanel is a relatively new drug with potential impact on the prognosis of patients with intractable focal onset seizures (Ledingham and Patsalos, 2013, Plosker, 2012), however there is at least one more report on similar observations of side effects in a patient with intellectual disability to what is reported here (Dolton and Choudry, 2014, Schulze-Bonhage and Hintz, 2015). This patient had normal intellectual ability, with no sign of depression.

To investigate the variations in suppression indices of patients and controls, box plot figures of individual participants were plotted in Figure 5.8 and Figure 5.9 and the between- and within-subject errors were calculated in Table 5.2. The results showed that patients had higher between- and within-subject errors. However, non-parametric tests indicated that the difference was not significant. One possible reason might be because of the small number of controls (n=4) compared to 16 patients in the longitudinal test. In addition, patients had repeated the test much longer than controls. This is worth investigating in a future study with more control subjects.

The purpose of this chapter was to investigate whether visual psychophysical tests could be a suitable tool for assessing seizure susceptibility at home. There were different problems that were impossible to overcome during this study, however are potential examples that must be considered for future studies. For example, small number of sample sizes in both groups. Specifically, for patients group the fact that 20 people with epilepsy were originally recruited and only 7 of them managed to finish shows how difficult it is to perform clinical research in epilepsy. All these patients were from the group of patients with frequent seizures, however in practice we could only capture a small number of seizures in each patient. Perhaps continuing the study could help increase this number, however it was not possible within the time frame of this study. In addition, despite all the efforts of the experimenter to make the task as user friendly as possible, yet some people with epilepsy found it difficult to work with.

In conclusion, results from this chapter showed that both control participants and patients with epilepsy has fluctuations in their suppression indices. Longitudinal data showed no strong link between timing of seizures and suppression indices in patients. Further non-parametric analyses showed no significant difference between variations in between subject and within-subject errors among patients and controls. Future studies are necessary to draw any strong conclusion.

Chapter 6 Results from India cohort

6.1 Introduction

One of the obstacles for recruiting patients in Newcastle was that recruitment was very slow. Therefore, as an addition to the original study, 56 patients and 25 healthy controls were recruited as part of collaboration between Institute of Neuroscience (IoN) in Newcastle and the Institute of Neurosciences Kolkata (INK) in India (INK; http://www.neurokolkata.org/). Patients' recruitment was done by Dr. Jenny Read and collaborators in India.

In this chapter I present results of 56 patients with confirmed epilepsy (37 male; average age: 33.7; range: 17.9-64.6) along with 25 healthy controls with age and sex matched to patients (17 male; average age: 30.65; range: 18.16-60.5). Patients with epilepsy were confirmed based on their medical history and neurological examination from epilepsy clinics of INK. Control participants were recruited from staff of INK or the accompanying family members. Further information about the patients are listed in Appendix 3 . The general analysis followed that performed on the Newcastle cohort, but these are presented separately because of subtle differences between the India and Newcastle data sets.

6.2 Significant relationship between motion suppression indices with age, but no relationship between contrast suppression indices and age in the India cohort

Figure 6.1 shows duration thresholds of 55 patients with epilepsy and 25 healthy controls in India. Indian patients and controls showed higher durations thresholds compared to those in Newcastle (Figure 6.1 compared to Figure 4.3). Next the relationship between motion suppression index and contrast suppression index were investigated. Similar to results of Newcastle, there was a significant relationship between motion suppression indices and age in both patients and healthy participants. Figure 6.2 shows the regression lines with p=0.013 for healthy controls, and p<0.001 for patients.

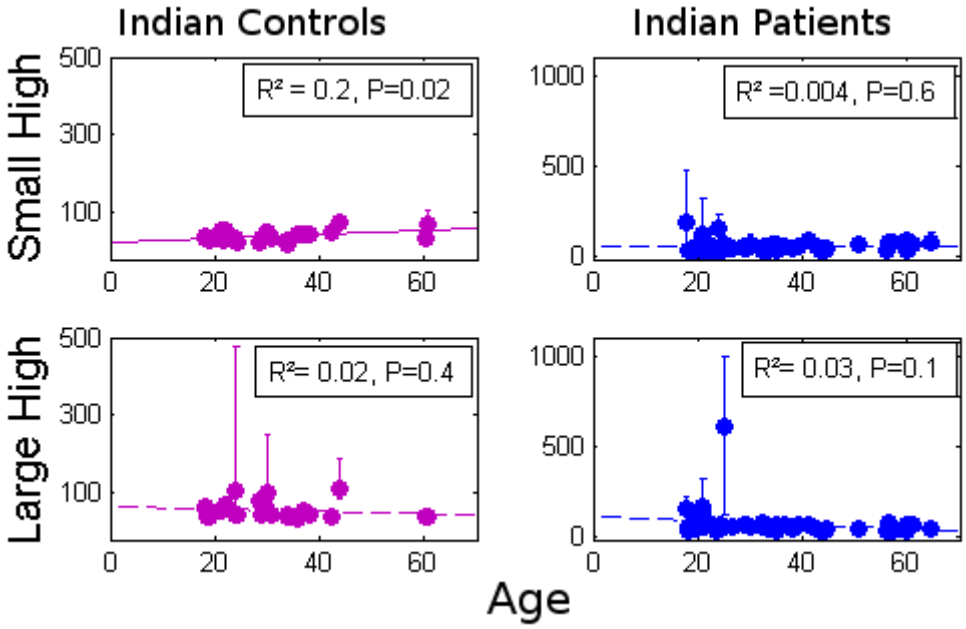


Figure 6.1. Duration thresholds of 25 controls and 55 patients with epilepsy in India as a function of age. Error bars show 95% confidence intervals. Lines show regression with age; solid line is where the regression of duration threshold with age is significant, dashed lines where it was non-significant. R^2 and p values are marked in each panel.

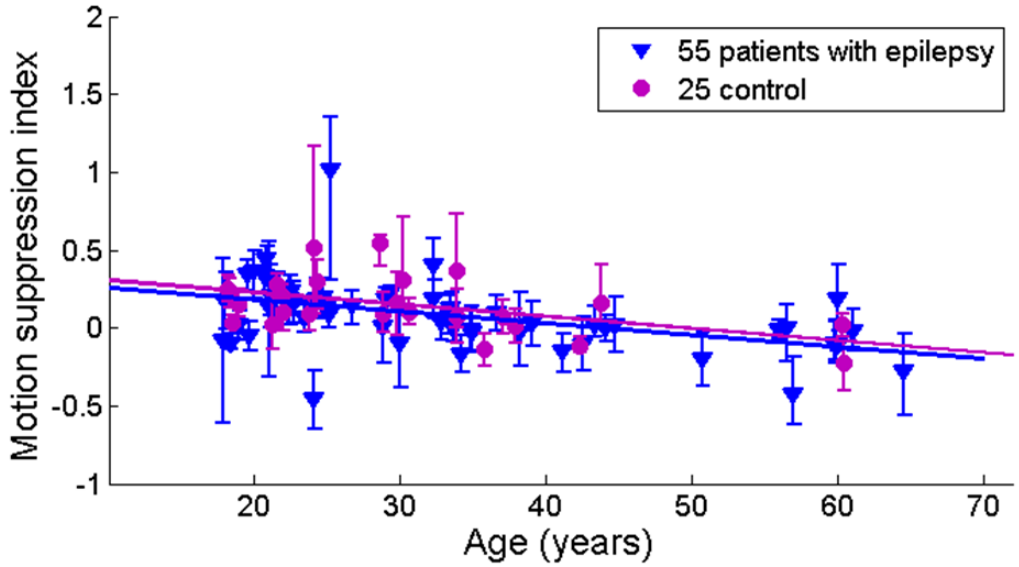


Figure 6.2. Motion suppression index as a function of age for 55 patients with epilepsy (in triangles) and 25 healthy participants (in circles). There was a significant relationship between suppression indices and age in both groups. For patients: Index=-0.0075*Age(in years)+0.3317, R^2=0.217, P<0.001, For controls: Index = -0.0077*Age(in years)+0.3804, R^2=0.238, p=0.013.

Figure 6.3 shows contrast thresholds for controls and patients in India. Indian patients and controls show higher contrast thresholds compared to participants in Newcastle. Similar to Newcastle, patients and controls in India showed more variability and higher thresholds in the parallel condition.

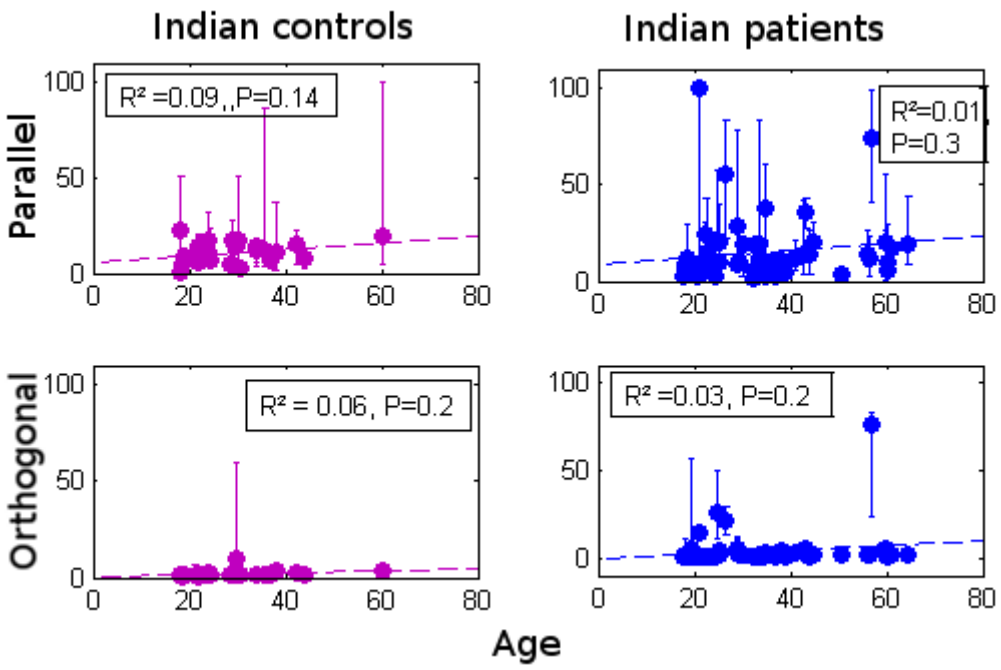


Figure 6.3. Contrast thresholds of 25 controls and 55 patients with epilepsy in India as a function of age. Error bars show 95% confidence intervals. Lines show regression with age; solid line is where the regression of contrast threshold with age is significant, dashed lines where it was non-significant. R^2 and p values are marked in each panel.

Figure 6.4 shows contrast suppression indices as a function of age and consistent with results in Newcastle, there was no significant relationship between age and contrast suppression indices in both patients and controls). This further confirms the differences between the two tasks that were further shown in Newcastle.

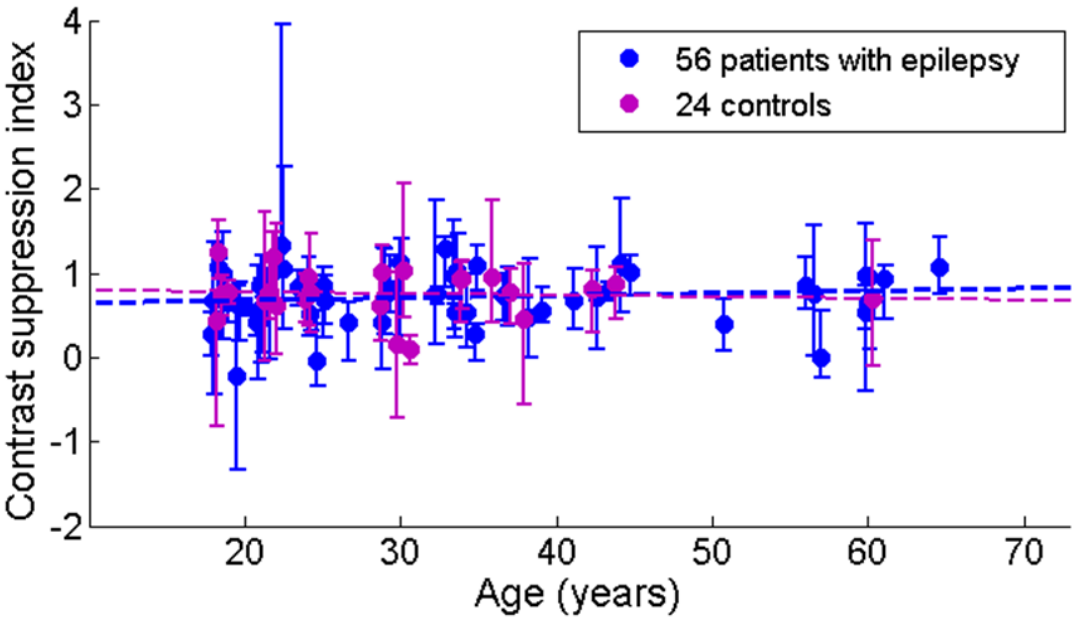


Figure 6.4. Contrast suppression index as a function of age for 56 patients with epilepsy (in blue) and 25 healthy participants (in purple). There was non-significant relationship between suppression indices and age in both groups. For patients: patients Index=-0.002*Age (in years)+0.6144, R^2=0.016, P=0.35, for controls: Index=-0.002*Age(in years)+0.813, R^2=0.005, p=0.75

6.3 Significant difference in suppression indices between patients and controls in Newcastle and India

Average of indices of patients and controls in Newcastle and India were plotted for the motion discrimination and contrast detection tasks in

Figure **6.5**. Suppression indices of patients and controls in India were greatly lower for the motion discrimination task relative to participants in Newcastle. This was also observed in Figure 6.1 which shows patients and controls in India have shorter duration thresholds compared to participants in Newcastle.

In addition, contrast suppression indices were higher in comparison with motion suppression indices at both Newcastle and India. And, while mean of contrast suppression in healthy control subjects is lower than patients in Newcastle, controls in India showed higher mean of contrast suppression index. The difference in mean of contrast suppression index of controls in Newcastle and India was significant with t=2.03 and p=0.003. Figure 6.3 shows that Indian controls and patients have higher contrast thresholds compared to participants in Newcastle.

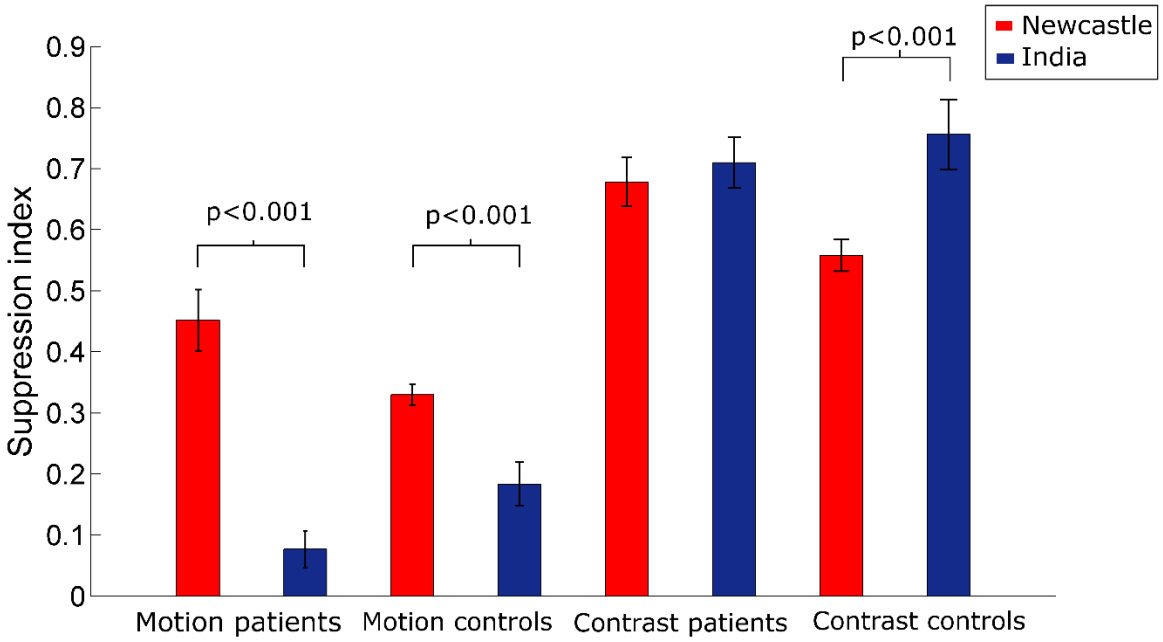


Figure 6.5. Comparison of motion and contrast suppression indices in patients and healthy control participants of Newcastle and India. Error bars are standard error of means.

Comparing summation indices, Indian controls had significantly higher summation index compared to controls in Newcastle (t-test; t=2.07, p=0.008) with average of 0.6 compared to 0.3. There was no significant difference in the summation indices between patients in India and Newcastle.

6.4 Analysis of psychophysics data with respect to seizure frequency in the India cohort

Individual suppression indices were plotted for each frequency scale (Figure 6.6) in both the motion discrimination and contrast detection tasks along with the controls. Average of each seizure frequency was then calculated and plotted on each scale (black diamonds). Age was found to have a significant relationship with the suppression indices in the motion discrimination task. Using a multiple regression analysis, age but not grading was found to be a significant predictor of motion suppression index (age: beta:-0.008, t=-4.8, $p<0.001$; grading: beta: 0.006, t=0.4, p=0.69). That is, on average motion suppression index decreases by 0.08 with each decade of age, similar to the decrease of 0.06/ decade found in Newcastle (Yazdani et al., 2015). The overall model explains 22% of the variance in the motion suppression index ($F(2, 74) = 11.8$, $p<0.001$, adjusted $R^2=0.22$). Therefore, I conclude that there is a non-significant correlation between the motion suppression index and seizure frequency, after controlling for the effect of age in India cohort (Figure 6.6, top panel).Multiple regression analysis showed that age and grading were not significant predictors of the contrast suppression index (age: beta=0.002, t=0.6, p=0.5; grading: beta=-0.011, t=-0.4, p=0.6).

Therefore, there is no relationship between seizure frequency and the contrast suppression index (Figure 6.6, bottom panel).

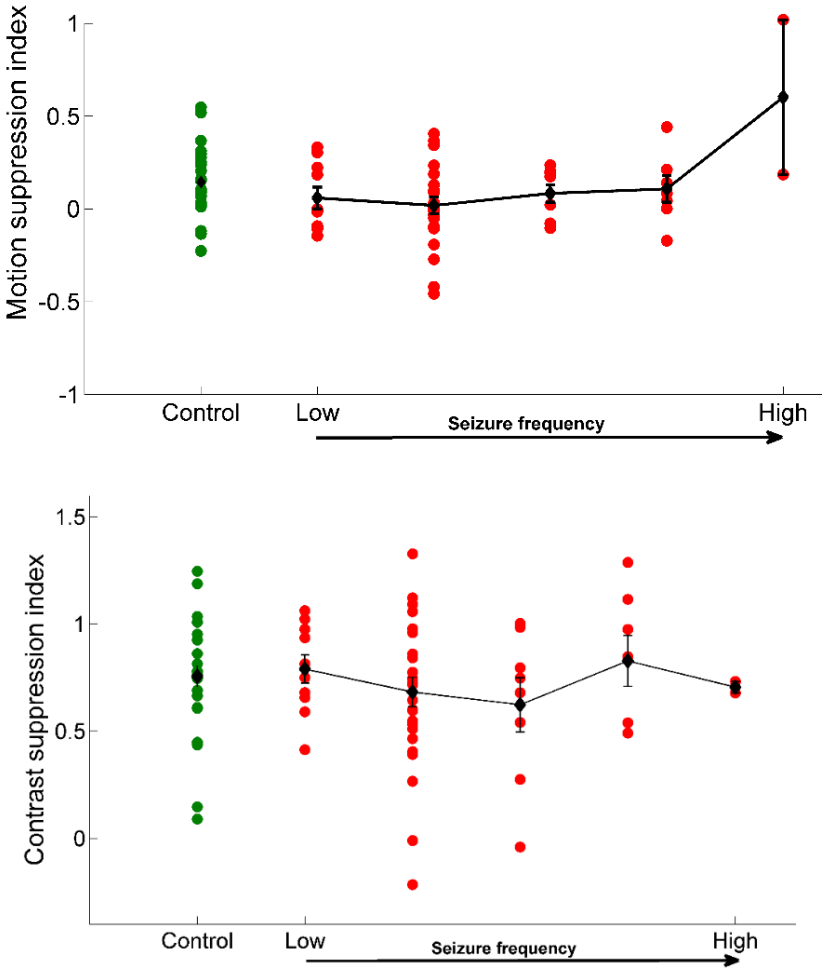


Figure 6.6. Suppression indices for patients in India as a function of seizure frequency. Top panel represents motion suppression and bottom panel contrast suppression indices for individual patients (red circles). Suppression indices of healthy controls are shown in green circles. Black diamonds represent average of suppression index within each group.

Similar to the analysis that was performed in Newcastle, patients from India were divided into two different groups of frequent and infrequent seizures according to their seizure frequency starting from 1 to 5 (based on Table 4.1-Grading A). In order to examine whether results of this grouping were robust, the same data but with the shifted threshold between the frequent and infrequent seizures were plotted and named as Grading B. Figure 6.7 and Figure 6.8 show the distribution of data as boxplot figures for Grading A and Grading B in the motion discrimination and the contrast detection tasks.

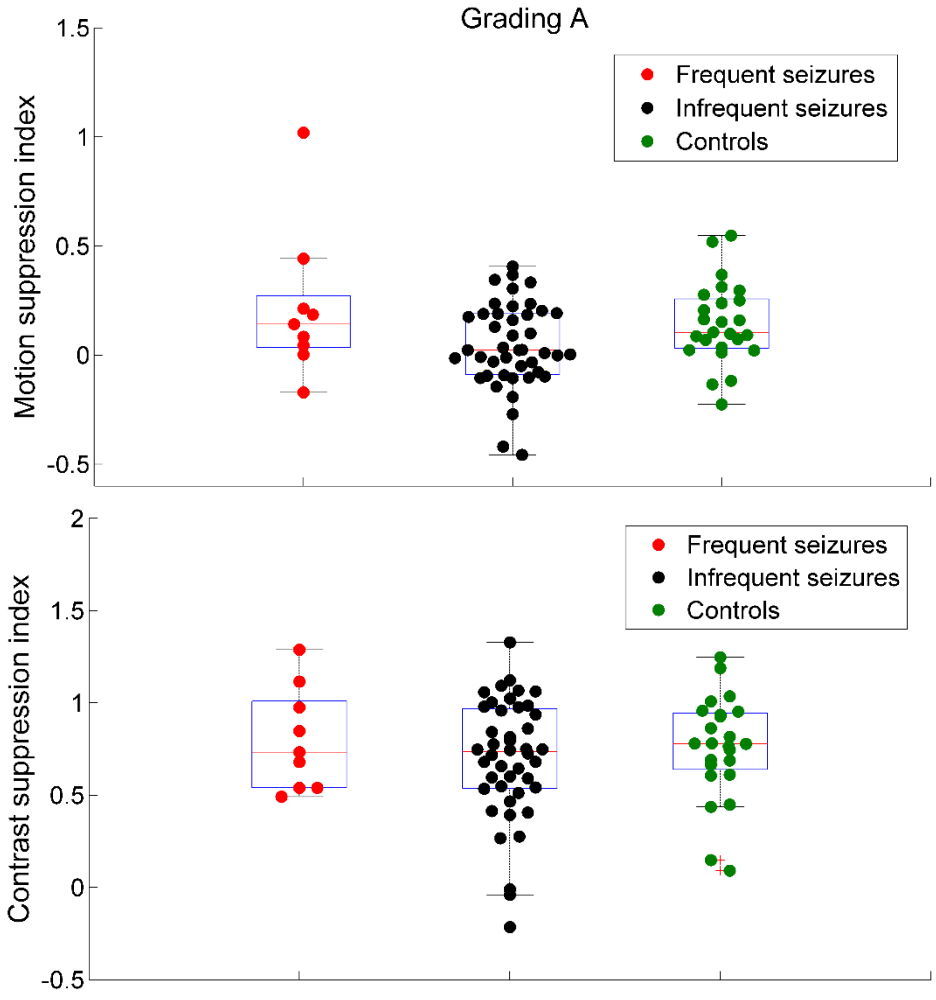


Figure 6.7. Boxplots of the motion and contrast suppression indices for Grading A of patients and controls in India.

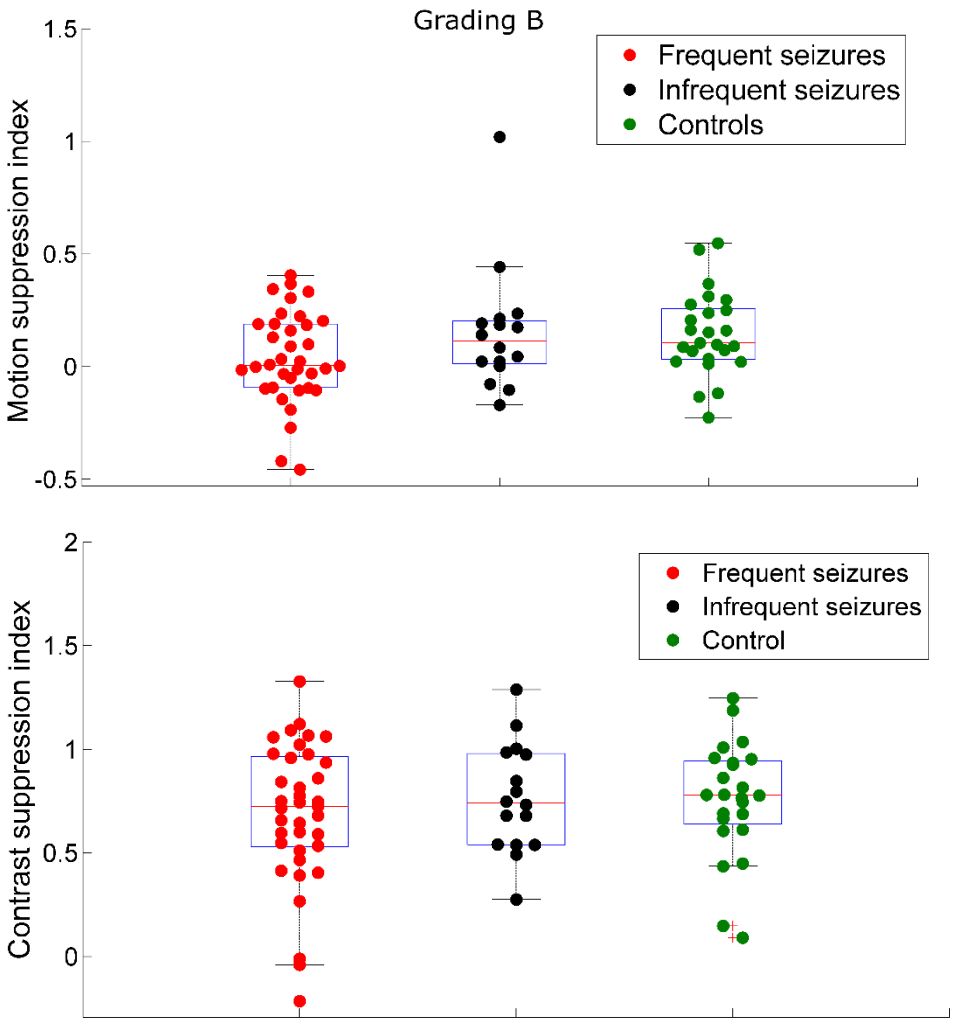


Figure 6.8. Boxplots of the motion and contrast suppression indices for Grading B of patients and controls in India.

6.5 No significant difference within the groups of controls, patients with frequent and patients with infrequent seizures in India cohort

Analysis of comparison between the indices in the groups of controls and patients with frequent and infrequent seizures are the following sections:

6.5.1 Results of grading A

There were 9 patients with frequent seizures, 43 with infrequent seizures, and 25 healthy controls in grading A. A significant regression equation for pooled data was found in the motion discrimination task ($F=23.37$, $p<0.001$), with $R^2= 0.23$ (Motion suppression index = -0.008*Age + 0.356), however regression analysis was non-significant in the contrast detection task ($p=0.538$). Scatter plot of residuals for the motion discrimination task is shown in Figure 6.9. This plot showed that the regression model was relatively good in capturing all the data points and data points were randomly scattered around the line of y=0. This figure pointed to two possible outliers in the population.

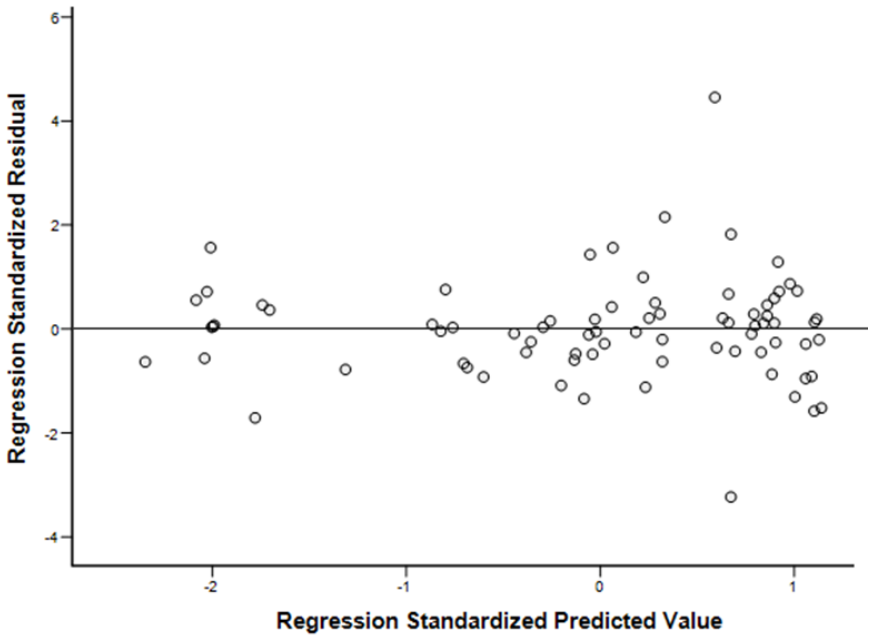


Figure 6.9. Scatter plot of residuals calculated from linear regression analysis for the motion discrimination task for 77 Indian participants. Predicted value by the regression model is on x-axis and the distance from horizontal line y=0 shows how well the model was for each data point.

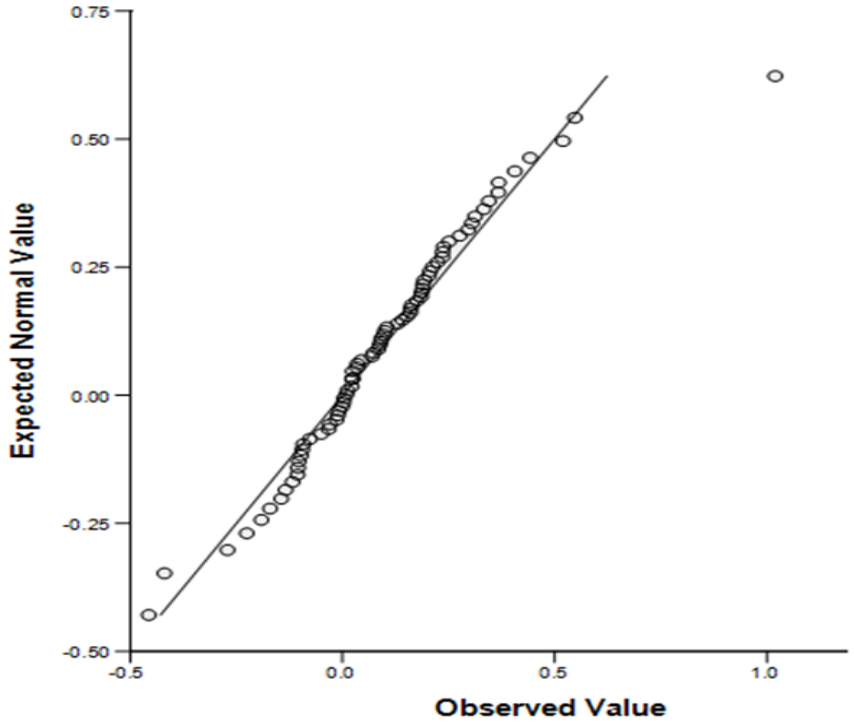


Figure 6.10. Q-Q plot of the motion suppression indices indicating a normally distributed data. Black circles represent all 77 Indian participants.

In order to check data normality, a Q-Q plot was created (Figure 6.10). This figure demonstrated that the population was normally distributed with most of the points aligned on the diagonal line. This figure also showed one likely outlier data point. Levene's test showed data was homogeneous ($p=0.876$). Therefore, as these data sets show a good approximation to a normal distribution ANOVA and ANCOVA tests were performed.

ANCOVA analysis further confirmed age to be a significant covariate ($F=20.1$, $p<0.001$). Further analysis showed no significant difference between the groups ($F=2.1$, $p=0.12$).

Q-Q analysis of the contrast detection task showed that data has a normal distribution (Figure 6.11), and therefore ANOVA analysis was performed to identify any possible differences within the groups. Data analysis showed no significant difference between the groups (F=0.6, p=0.6).

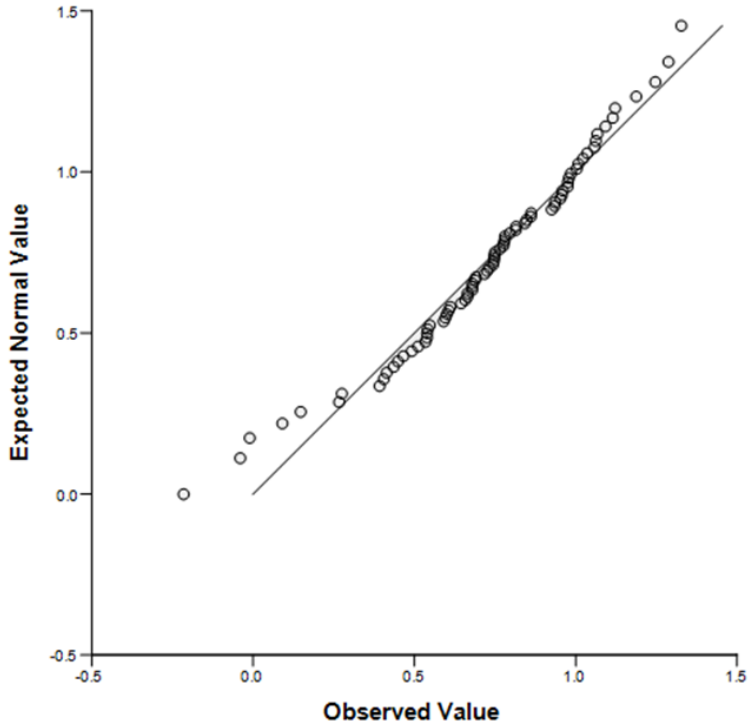


Figure 6.11. Normal Q-Q plot of the contrast suppression indices. Black circles represent all 78 Indian participants. Normally distributed data will lie approximately on the black straight line.

6.5.2 Results of grading B:

There were 17 patients with frequent seizures, 35 with infrequent seizures, and 25 healthy participants. Analysis of covariance (ANCOVA) confirmed age to be a significant factor in the motion discrimination task with $F=20.4$, $p<0.001$. Further analysis showed that there was no significant difference between the groups after controlling for age ($F=1.34$, $p=0.3$).

ANOVA analysis showed no significant difference within the groups in the contrast detection task, $F=0.47$, $p=0.63$.

Therefore, there was no significant difference within the controls and patients with frequent and infrequent seizures in India cohort.

6.6 Suppression index as a function of number of Anti Epilepsy Drugs (AED) in India cohort

As AEDs could be a possible confound, mean of suppression indices were plotted as a function of number of AEDs in India (Figure 6.12).

ANOVA analysis only indicated a significant difference between the mean of the motion suppression indices of patients who are on three AEDs compared to four with $p=0.05$.

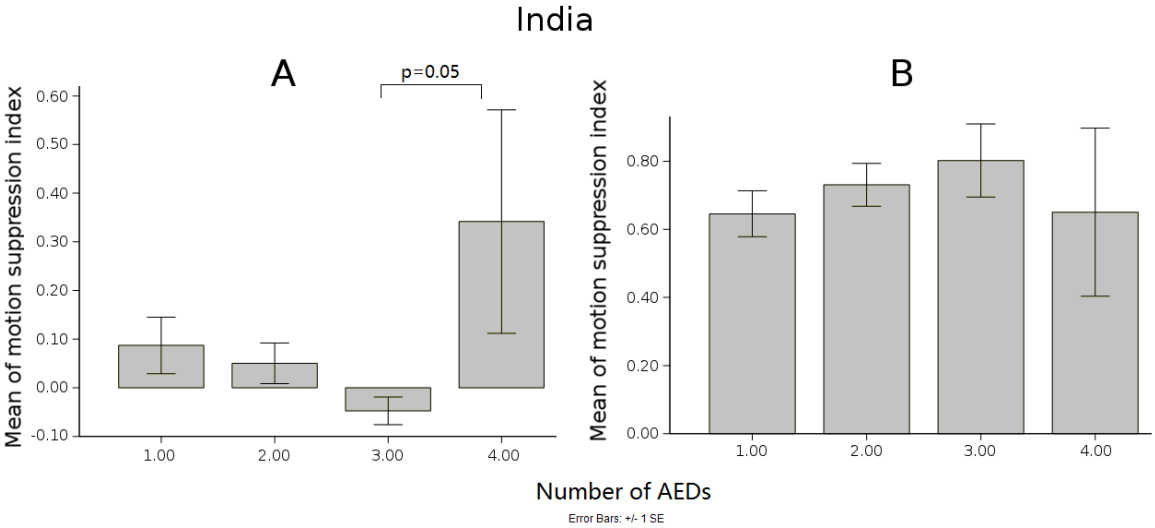


Figure 6.12. Mean of motion (A) and contrast suppression (B) indices as a function of number of AEDs. Error bars are standard error of means (SEM).

To explore the discrepancies observed between Newcastle and India, a group of 10 Indians (average age=30.1) who live in Newcastle were tested. They had spent from 10 years to several decades in India, and between 3 weeks to 14 years in Newcastle. The average of the motion suppression index in this group was around 0.27 which is very close to the average of control participants in Newcastle (0.3) and much higher than the average in India (0.14) (t=-1.9, df=33, p=0.06 (two tail)). It is worth mentioning that the p value of 0.06 is close to significance. A power analysis showed that recruiting 8 more participants would help achieve a definite answer (95% confidence interval, sample size=18).

6.7 Discussion

Analysis of patients in India did not show any significant difference between patients and healthy controls. Moreover, patients in India did not exhibit duration thresholds over 600ms. These findings were in contrast to some of the results found in Newcastle. Participants in India showed shorter duration thresholds and higher contrast thresholds compared to participants in Newcastle (Figure 6.1 and Figure 6.3).

ANOVA analysis indicated that the number of AEDs had a significant effect on the motion surround suppression indices (between 3 and 4 AEDs, $p=0.05$). However, this could be caused by the surprising negative mean of the motion suppression index in patients who were on three AEDs in India, or the high standard error of mean in patients with four AEDs.

Participants in India demonstrated a similar relationship with age in the motion discrimination and the contrast detection tasks to participants in Newcastle.

The mean of the motion suppression index in India was significantly lower than the measured motion suppression in participants in Newcastle in both patients and controls ($p<0.001$). In the contrast detection task, controls in India had significantly higher suppression indices compared to controls in Newcastle ($p<0.001$).

When considering the age differences between groups, a multiple regression analysis showed a non-significant relationship between the motion and contrast suppression indices and seizure frequency. The other observed difference between Newcastle and India was that patients in India did not show any duration threshold over 600ms. In addition, a group of 10 Indians who live in Newcastle were tested and showed very similar results to participants in Newcastle.

These intriguing differences in results between Newcastle and India are highly unlikely to be caused by differences in the device that was used, since it was a similar computer and program which was shipped to India. Moreover, control subjects who did the tests on both devices did not have significantly different results.

Other probable explanations might be in the differences with age or AEDs between groups in Newcastle and India. However, participants in India were actually younger compared to Newcastle participants. The average age of patients with epilepsy in India was 33.73 (range: 17.83, 64.6), compared to patients in Newcastle with 42.34 (range: 17, 82.3). Similarly, the average age of healthy controls in India was lower than the one in Newcastle. Details of information of Indian patients were also checked by an independent neurologist who confirmed that there were no significant differences in AEDs that were prescribed between Newcastle and India. And in any case this cannot explain the observed differences in the control subjects. It should also be noted that these patients in India were seen at a clinic which has the standard of a western hospital (INK; http://www.neurokolkata.org/) specifically in terms of expertise and diagnostic tests.

One potential reason for the observed differences could be that infective causes are a bigger proportion of Indian cases (Amudhan et al., 2015) due to inadequate resources, lower income and education and the low importance given for public health aspects of epilepsy. Another possibility might be in dietary differences; a recent short study done by Baker et al. (2015) demonstrated that yeast extract as a GABA precursor could affect neural responsivity. They measured visual evoked potentials in fourteen participants with sine wave gratings flickering at various contrasts. Then the same stimuli were tested on them after consuming marmite for four weeks. They showed that this intervention reduced neural

responses at higher contrasts by up to 20%, but did not change the baseline activity to a blank screen. Nevertheless, this is a very preliminary study only reported at the European Conference on Visual Perception (ECVP 2015). Other studies showed black cumin (a major ingredients in Indian food) might have effects on reducing excitability, induction of seizures and improving adverse effects of AEDs (Ezz et al., 2011, Bhandari, 2014, Hosseinzadeh and Parvardeh, 2004, Akhondian et al., 2007). Another study reported Rhizoma Curcumae, a common Chinese dietary spice, as an anti-convulsive agent (Ding et al., 2014).

All these studies point to possible effects of diet on cortical inhibition, however more investigation is necessary to draw any strong conclusion.

Chapter 7 General discussion

7.1 Overview

There are several studies investigating the role of inhibition in maintaining proper dynamics of neuronal networks in the cortex with a great range of computational models (Ledoux and Brunel, 2011), experimental techniques (Muldoon et al., 2015) and novel genetic approaches (Dhindsa and Goldstein, 2015, Guerrini and Noebels, 2014). A lot of efforts have also been made to find a way to predict seizures (Freestone et al., 2015) and improve the lives of patients. Although substantial progress has been made by a close relationship between clinical, computational and basic epilepsy research in recent years, research into human epilepsy is still facing a lot of limitations. There remain many questions about the process of seizure generation, termination, and even how the anti-epileptic drugs work, but in particular, one significant obstacle in seizure prediction is that most of the approaches are invasive and still not accurate enough to predict a seizure.

Endogenous inhibitory mechanisms are believed to restrict the spread of epileptic discharges in cortical networks. Similar inhibitory mechanisms also influence physiological processing. Therefore, we used psychophysical assays of these physiological processing to gather information about the quality of inhibitory restraint in individuals with epilepsy. Visual psychophysics is a fascinating tool to study the relationship between physical properties of a stimulus and its perception non-invasively (Pelli and Farell, 2010). Comparing similar patterns of results in the neurophysiology findings to psychophysical results, helps experimenters to speculate about the specific neural substrate.

There are different visual psychophysics paradigms which are believed to measure cortical inhibition (Tadin, 2015, Tadin et al., 2003) and the aim of this

thesis was to probe some of these methods to investigate whether they could be used as a potential tool to predict a seizure in patients with epilepsy. In fact visual psychophysics tests have been explored in other clinical disorders such as schizophrenia (Tadin et al., 2006, Serrano-Pedraza et al., 2014), autism (Koldewyn et al., 2010) and depression (Golomb et al., 2009). However, here for the first time visual psychophysical measures of surround suppression have been investigated in epilepsy as a way of monitoring and improving treatment. Our hypothesis was that if seizures are generated due to the reduction in inhibition, then psychophysical evidence of this could be expected to be observed as a reduced surround suppression index in patients with epilepsy. If so, it may be manifest not only as a difference between controls and patients, but also as a change leading up to a seizure so that it might be used also for prediction rather than diagnosis. The idea was that we want to have a simple non-invasive method with minimal instructions to set up and run for individuals with epilepsy to measure their suppression index for the day and determine how it compares to their general average to aid clinical management. This approach must meet several requirements, such as be able to predict seizures arising from any part of the brain, be accurate and does not produce too many false positives, gives enough time for the patients to respond (for example take extra AED), ease of use and the ability to do it at home.

Three different psychophysical paradigms were explored; the motion discrimination task in which duration thresholds were measured in high (82%) and low contrasts (2.5%), the contrast detection task in which contrast thresholds were estimated when the stimulus was surrounded by a stimulus of parallel and orthogonal orientations to the background stimulus, and the orientation discrimination task in which orientation thresholds were calculated.

These methods produce a suppression index which is suggested to reflect cortical inhibition. However it has not been clearly established that these suppression indices really relate to any aspect of cortical inhibition, and even if they all do, it remains possible that they reflect different aspects of cortical inhibition. For instance they might measure cortical inhibition of different areas of the cortex. Hence, a way of testing whether these suppression indices do reflect similar aspects of cortical inhibition is to examine whether they are correlated across a population of different individuals.

In Chapter 3, I presented these results from a subgroup of healthy controls who did both the motion discrimination and the contrast detection tasks following each other in the same condition (similar room lighting, distance, time of the day). The goal of this chapter was to try to answer the first aim of this thesis which was to investigate whether or not these different paradigms of surround suppression reflect the same property of the visual cortex. Results indicated for the first time that the motion and the contrast suppression indices that are widely linked to cortical inhibition in a range of studies were actually not significantly correlated and are measuring different aspects of cortical function. What this finding shows is that the surround suppression indices that are widely used in the literature are in fact not the same and must be used cautiously. We found the motion discrimination task to be a more effective task in terms of showing differences between controls and patients and in particular in respect to patients' types of seizures. Moreover, I reproduced the previously reported correlation between age and the motion discrimination surround suppression index (Betts et al., 2005). The contrast suppression index however was not correlated with age. This was another evidence to show the lack of correlation between the two indices.

I also found that the summation index declined with age at a rate of 0.008 per year. Control subjects similar to results of Tadin et al. (2003) had longer duration thresholds for the large gratings in high contrast, but shorter duration thresholds in low contrast. Chapter 3 demonstrated that motion and contrast suppression indices are not measuring the same property of the cortex. However, for the study of epilepsy because we did not know which measure reflects the network relevant in epilepsy we included both of the tests to investigate whether either, neither or both show a correlation with frequency of seizures. To do so, patients' suppression indices in the motion discrimination and the contrast detection tasks were divided based on two grading (Grading A and B) into patients with frequent and infrequent seizures. Since GABAergic blockade is one of the basic causes of seizures and epilepsy (Curtis et al., 1970, Schevon et al., 2012), we hypothesised that suppression index measured by visual psychophysics may perhaps indicate a relationship between the reduced suppression index and higher frequency of seizures. Using non-parametric analyses we showed in chapter 4 that patients with higher frequency of seizures tend of have higher amount of suppression index in the motion discrimination task. However, multivariate regression analyses showed that frequency was not a significant factor (Table 4.4). This lack of effect of seizure frequency was better observed when frequency was plotted for the three seizure subtypes individually (Exclusively focal, focal seizures evolving into bilateral convulsive and GGE, Figure 4.22). These plots showed that, patients with exclusive focal seizures tended towards a higher seizure frequency. This mismatch in the seizure frequency between the groups was the reason to distort my interpretation of the effect of frequency in the preliminary analysis of the data. Therefore, we concluded that there is a relationship between suppression index and the likelihood of seizure generalization and a lack of relationship with seizure frequency. This was importantly different to what we previously anticipated in

which people with epilepsy would have a reduced suppression index (SI), indicative of lowered inhibitory restraint. Instead, we found that as a group, patients with generalised seizures are no different from control participants, but those with focal epilepsy with no generalization have a raised SI (Figure 4.20 and Figure **4.21**). The significantly raised suppression index in patients with focal epilepsy, relative to the other epilepsy groups, could not be explained by differences in age or IQ. And while we cannot fully discount a confounding effect of concurrent depression, this condition is not known to be differentially associated with the presence, or absence, of generalised seizures in patients with focal epilepsy. Drug interactions were difficult to assess because the diverse drug regimes in our patient cohorts made it difficult to control for this variable. Since the SI is considered to reflect cortical GABAergic interactions, we performed several different analyses to compare drugs that are known to modulate GABAergic activity and showed that the different epilepsy cohorts had broadly similar pharma-profiles. There was also no apparent difference between patients with high and those with low suppression indices. It remains a possibility that some AEDs may interfere with performance on the test, but this is highly unlikely to explain the differences between the epilepsy groups.

Multiple regression analysis for the contrast detection task, showed that age and grading were not significant predictors of the contrast suppression index (age: beta=0.001, t=0.5, p=0.6; grading: beta=0.078, t=1.55, p=0.13) and reported none significant relationship between seizure frequency and the contrast suppression index (Figure 4.19). This result also provide further evidence to show that the motion and the contrast suppression indices are not measuring the same property of the cortical inhibition.

The association of SSI with age persisted in all groups and the largest increases of SI were found in young patients without a history of seizure generalisation. This group showed a significantly steeper association which may represent a progressive change in the risk of seizure generalization; undoubtedly some people in this group will at some stage in their life experience a generalized seizure, meaning that they would have moved epilepsy groups in our analysis. At an early age, then, these people might be considered “latent” with respect to seizure generalization.

Furthermore, in chapter 4, given the association between seizure generalization and SUDEP, and the fact that currently there is no reliable biomarker of SUDEP before the occurrence of a generalised seizure, we divided patients based on a history of GTCS and compared them against each other and the control group. Results showed a significant difference between patients with focal seizures and all the other groups. Specifically, patients with exclusive focal seizures had higher average of motion suppression index and patients with focal seizures evolving into bilateral convulsive seizures had the lowest suppression index (Figure 4.23). We suggest that the suppression index may prove to be a promising candidate for a SUDEP biomarker: the raised SI seen in patients who have never previously had a generalised seizure indicating a lower risk of SUDEP, whereas the normal SSI seen in patients with a history of generalised seizures indicating a higher risk. Since SSI also tends to decrease with age, this index will be most useful for patients who develop, or are diagnosed, epilepsy early in life. This could be interpreted that patients with focal seizures, might have an ability to increase inhibition as a response to a seizure focus and therefore are less likely to develop a generalised seizure and suggest that patients with higher suppression index (stronger inhibition) are potentially in less risk of SUDEP.

One of the main hypothesis of this thesis was whether visual psychophysics could be used in a clinic to help with managing patients care. These tests are simple and non-invasive, however it takes time and patience for the patients to learn them. However, it might one day be possible to use this as a tool in clinics to measure the risk of SUDEP in patients who might be in the risk of SUDEP. It might be easier and less time consuming to ask a patient whether he or she has a history of GTCS, however experience shows that in a lot of cases there might be no witness at the time of a generalised seizure (the patient might even be not aware of it) and also it is beneficiary to have a tool to warn the neurologist about the risk factor before the generalised seizure has actually happened. Again, for a more robust conclusion longitudinal studies of progression and variability in SI in individuals with epilepsy is necessary.

These results validated the potential usefulness of these tests in epilepsy management, and so motivated the second aim of this thesis which was to investigate whether visual psychophysical tests could be used for predicting seizures. To investigate whether suppression indices change in relationship to a seizure, we performed longitudinal tests in sixteen of the patients.

There were a lot of practical difficulties in collecting data for longitudinal tests. Firstly, finding patients who would agree to run the tests in a long run was difficult. This was less anticipated considering the short length of the tests (10 minutes for each run) and the fact that patients had the freedom to adapt the time of running the tests into their lifestyle. Secondly, two patients reported to feel dizziness and agitated after a couple of days of start. One of these patients (male, 29 years old, diagnosed with focal dyscognitive seizures for the last ten years, medication: Lamotrigine and Topiramate) was recruited through a local epilepsy support group and I did not have access to his full medical history to accurately assess his condition. He reported to have had one seizure every 6

weeks prior to doing the test, but then reported a sudden increase in seizure frequency, and so after doing five rounds of tests, decided to stop. The second patient (Male, 50 years old, diagnosis: temporal lobe epilepsy with focal dyscognitive seizures with possibility of absence seizures for the last 2 years; Medication: Levetiracetam) did not report any problems until his medication was increased. His family felt that the experiment was causing him stress, and he decided to withdraw from the experiment. Change of medication and psychological problems had a strong role on declining from participation in these two patients. Thirdly, some patients with reportedly frequent seizures did not have any seizures in the longitudinal process. These patients had seizures at least twice a month and yet had no seizure in the course of participation. This might have caused by poor previous report of these patients' seizures, or the fact that these patients might have been more mindful of their epilepsy and consequently took their AEDs more regularly. And lastly, a lot of the recruited patients were not keeping a precise record of their seizures even after recommending them to do so. Different methods were discussed with patients, such as keeping a record in a diary, note taking using their phones and different phone applications. At least one of them had mainly night time seizures (nocturnal seizures). These problems along with the fact that the experimenter had minimal control over the condition of the room where the test was done and that recruitment had to be done via the usual clinical team made it challenging to increase the accuracy of the conclusions.

The hypothesis of the longitudinal test in chapter 5 was to investigate the possibility of observing a different pattern in the measured suppression indices leading to a seizure and to investigate if this change can be used as a way of determining the time of seizure occurrence. In other words to investigate whether these tests could be a possible approach to predict patients' seizures in

practice. A lot of the current approaches need patients to be connected to an electroencephalogram (EEG) or go through surgically placed implants which are in long run impossible or with a lot of implications. We reported that both controls and patients had fluctuations in their surround suppression indices in the motion discrimination and the contrast detection tasks. This was not only among different days, but also during different times of a day, however there was no clear pattern that reliably predicted when a seizure was likely to occur. The observed variability of suppression indices in controls could indicate that reduction in inhibition is not on its own enough to cause seizures and that the level of inhibition always remains significantly higher than the threshold for producing a seizure. In order to assure stable periods of activity in the cortex a balance interplay between recurrent excitation and inhibition is necessary (Shu et al., 2003, Schevon et al., 2012). Studies suggest that local cortical networks apply proportional inhibition in response to increasing excitation (Shu et al., 2003). Therefore, the observed fluctuations in controls could be in fact the interplay between excitation and inhibition. As it was explained by Isaacson and Scanziani (2011) the idea of a balance between excitation and inhibition does not mean that these two forces are equal. They are not equally distributed along the soma and dendrites of neurons and therefore their ratio depends highly on the place that it is being measured. Acute experimental manipulation has showed that excitation and inhibition have a highly dynamic ratio and an overall proportionality. This interaction between excitation and inhibition and the activity in the seizure focus could similarly explain the observed higher amount of suppression index in the patients with frequent seizures. One plausible idea is that a seizure focus drives increased activity in the inhibitory surround. If the seizure focus is possible to be maintained by the increased activity in the surround, then the seizure remains focal, but if this breaks down or was unable to respond to the focal activity in the first instance, a generalised seizure could

occur. It is also possible to hypothesise that some global issue with inhibition underlies a tendency for focal seizures to generalise.

Having demonstrated that inhibition fluctuates in controls, the question was whether this fluctuation is different in patients. In other words, it may be not the absolute level measured at a single time point, but how much it changes (for example goes below the threshold for triggering a seizure) that matters. Results of measuring standard deviation of between and within subjects indicated that although patients showed higher variations compared to that shown by the control group, the difference was not significant.

The next question to answer was whether there is any association between the measured fluctuations in the suppression indices and times of seizures. To answer this question, we decided to compare suppression indices in defined cut offs (24hr, 12hr, 6hr before or after a seizure) using box plots. Boxplots did not show any relationship between the suppression indices and timing of seizures in any of the time points. The outcome is that we have not been able to find a strong link between timing of seizures and suppression index and considering the few number of samples of controls and patients we cannot use this information to predict the occurrence of a seizure.

There are multiple mechanisms involved in seizure generation. Results of decades of experimental investigations in animals have given rise to the idea of an imbalance of inhibition and excitation in seizure development (Staley, 2015, Prince and Wilder, 1967, Wiechert and Herbst, 1966, Matsumoto and Marsan, 1964). The idea of imbalance between excitatory and inhibitory drives might explain seizure generation, however it cannot always explain epilepsy, the chronic condition giving rise to seizures. The brain activity in patients with epilepsy has a great dynamic range with most of the time being normal. For example, the amount of time that the brain seizes is relatively small (<< less than

1%, typically) (Staley, 2015, Moran et al., 2004). If the whole network undergoes a lack of balance of excitation and inhibition, then why does that network not seize all the time? Perhaps, it is reasonable to think that there are further mechanisms associated with inducing or blocking seizure activity which leads to epilepsy.

Positive feedback mechanisms, the process of enhancement of an effect, might be an additional influence on the system. Once a seizure was induced, given that there are enough positive feedback in the system, the seizure itself can produce enough activity to suppress inhibition or increase excitation (Abbott et al., 1997, Staley, 2015, Scharfman, 2007). For example according to the potassium accumulation hypothesis, an initial increase above a certain threshold boosts extracellular potassium accumulation which in turn triggers a positive feedback loop, with increased excitability, increased firing, and further K^+ increases (Frohlich et al., 2008, Fertziger and Ranck Jr, 1970). As another example whilst PV interneurons have been shown to have inhibitory effects on epileptic activity, in other situations they can actually prompt seizures (Ellender et al., 2014). Cl^- accumulation can change the role of PV^+ interneurons to fire rather than terminate hyperexcitability in the network during the clonic phase of a seizure (Sessolo et al., 2015, Cohen et al., 2002, Dzhala et al., 2005).

Although visual psychophysical tasks have been used in a variety of clinical disorders, there are still some discrepancies in the literature. An example is in studies done in schizophrenia. While a lot of studies in patients with schizophrenia have reported reduced surround suppression in judgements of relative contrast (Dakin et al., 2005, Serrano-Pedraza et al., 2014, Yoon et al., 2010, Yoon et al., 2009) and motion (Tadin et al., 2006), a study done by Chen et al. (2008) indicated elevated amount of suppression in patients with schizophrenia compared to healthy controls in a random dot motion stimuli.

These dissimilarities in comparing reports for schizophrenia could be caused by different paradigms or patients groups that have been used. Similarly, as I showed in chapter 3 that motion and contrast suppression indices are not correlated, we cannot merge the findings of different psychophysical tasks and expect them to show similar results. Moreover, it is still not clear whether visual psychophysics (even by using the same task) have the consistency to be used as a tool for studying different clinical disorders. Another important factor is that neural suppression consists of different range of inhibitory processes and the relation between suppression and cortical inhibition is greatly complex (Friedman and Miyake, 2004, Tadin, 2015). Therefore, it is crucial to be very clear on which tasks are being used and what they actually measure.

7.2 General discussion of results in India cohort

Results found at India cohort was different in several ways to participants in Newcastle. Firstly, there was no significant difference between controls and patients with frequent and infrequent seizures in India. Secondly, no patient had duration thresholds higher than 600ms. And finally, the mean of the motion suppression index in India was significantly lower in both patients and controls, and the mean of the contrast suppression index was significantly higher compared to Newcastle. These results are difficult to interpret at this stage. One possibility is that a long term exposed factor to participants in India might have a role in the observed variances, such as dietary and sun exposure and its effects on the contrast sensitivity. The higher incidence of infectious diseases and their association to epilepsy could also be a potential reason for the observed differences. I was not in a position to explore these any further within the time frame of my thesis. In the future, a more accurate design of the study should be carried out with enough power and sample size to find a more clear answer.

Running psychophysics and patients' recruitment require careful observation and patience of the experimenter.

7.3 Future work

A long list of possible follow-up experiments could be envisaged in studies using psychophysics. For instance, one may wonder what information do high duration thresholds in the motion discrimination tell us and why some people had these long durations. A way to find possible answers for this particular question is to first find out how reliable these extreme results are with repeating these psychophysical experiments in the participants who showed these high duration thresholds, and then use a different experimental approach to test them. A method of constant stimuli is one option to test high stimulus durations repeatedly with randomly interleaved staircases. If this method gives similar results to the previous approach, then it is necessary to look at individual psychometric functions to extract more information.

Moreover, we still do not have enough evidence to know what exactly these visual psychophysical tests measure. To find more evidence, different studies with combination of visual psychophysics with simultaneous EEG, Magnetic Resonance Spectroscopy (MRS) or Transcranial Magnetic Stimulation (TMS) could be defined to compare the findings and get a more clear understanding of the neuronal processes in the brain. Another interesting line of investigation is to explore the possible reasons of why Indians did not show similar results to participants in Newcastle. What are the differences between the two cohorts that Indian participants never showed high duration thresholds? Could dietary and contrast sensitivity be accounted as possible reasons for the observed differences? One way of finding answers to these questions is to use different psychophysical approaches. Another possible option is to use visual evoked

potentials to measure the contrast gain control of patients in response to patterns of different contrast and look for possible differences between patients in Newcastle and India. Park and Tadin (2015) presented an abstract at the Vision Sciences Society (VSS) meeting showing that people with higher amount of suppression index were better at segmenting motion defined figure-ground stimuli. They suggested that there is a trade-off and different people adopt different optima. Maybe the optima balance is different in India than in Newcastle for some reason we do not understand.

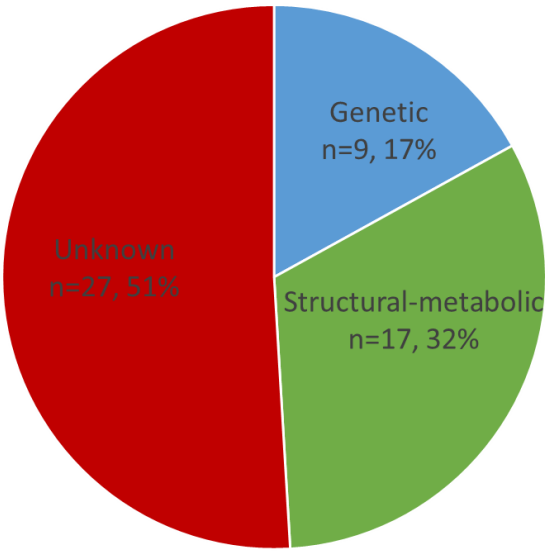
In conclusion, results from this study revealed that the motion discrimination and the contrast detection tasks are not measuring the same property of the cortex. For the epilepsy cohort, our prior hypothesis was that people with epilepsy may show a reduced suppression index. However, most showed similar suppression indices to our control group, whilst one group of patients, those with exclusively focal seizures, actually showed an increase.

In addition, I report the first instance of raised suppression index in any patient cohort, which appears to differentiate between patients with respect to the likelihood of seizure generalization. Results suggest that the motion suppression index may prove to be a promising candidate as a biomarker to predict the risk of SUDEP in patients with epilepsy. Raised motion suppression index seen in patients who have never previously had a generalised seizure can indicate a lower risk of SUDEP, whereas a normal motion suppression index in patients with a history of generalised seizures can indicate a higher risk.

Appendices

Patients' information:

Patients' aetiology of epilepsy is shown in the pie chart Appendix 1 (Fisher et al., 2014).



Appendix 1. Patients' classification of aetiology.

Appendix 2. Table of patients' information. Including patients ID, duration of epilepsy (EP duration), PMH (Past Medical History), imaging results, types of seizures, presumed aetiology, presumed location, information regarding their grading and whether they belong to defined frequent and infrequent groups and their grade, details of the frequency of seizures, anti-epileptic drugs (AEDs), and the number of AEDs.

ID	Age onset	Ep duration	PMH	Imaging	Seizure type	Presumed aetiology	Presumed location	Grading A	Grading B	GRADE	Detail of frequency	AED	Number of AEDs
EP1	Not known	Not knows	-	R MTS	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Frequent	3	2-3/month	VPA-Epanutin (PHT)-CLB-PGB	4
EP2	13	40	Meningitis/encephalitis as child	L MTS	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Infrequent	1	None since Aug 2010- seizure free for 4 years	CBZ/CLOB	2
EP3	12	40	Intracranial tuberculoma	Left temporal lobe atrophy	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Infrequent	1	None since Oct 2005	CBZ/KEP/LAM	3
EP4	64	8	Aortic valve replacement	Normal (CT)	Focal dyscog	Unknown	Temporal	Frequent	Frequent	4	1/week	LAM	1
EP5	34	0.5	Head injury/frontal lobectomy	Bilateral Frontal encephalomalacia	Focal motor	Structural-metabolic	Frontal	Infrequent	Infrequent	2	None for 2 months, previously 1/month	CBZ	1
EP6	11 months	>20	Amygdalo-hippocampectomy 2012	L MTS	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Infrequent	2	None for 5 months, previously 2/month	VAL/LAM/PREGAB/CLOB	4
EP7	6	>50	Skull fracture	R MTS	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Frequent	3	1/month	PHE/LAM/LEV	3
EP8	childhood	30	-	n/a	GTCS	Genetic	Generalised	Frequent	Frequent	5	Daily	none	0
EP9	12	5	-	Normal	GTCS	Genetic	Generalised	Infrequent	Infrequent	1	Single seizure	VAL	1
EP10	16	0.5	-	n/a	GTCS	Genetic	Generalised	Infrequent	Infrequent	2	0.5/month- 3 in 6 months	VAL	1

ID	Age onset	Ep duration	PMH	Imaging	Seizure type	Presumed aetiology	Presumed location	Grading A	Grading B	GRADE	Detail of frequency	AED	Number of AEDs
EP11	54	<1 year	-	Normal	GTCS	Unknown	Unknown	infrequent	infrequent	2	2 since Sep 2012- 2 in 6 months	VA 400mg started 16/01/13	1
EP12	18	Single seizure	-	Normal	Bilateral convulsive	Unknown	Occipital	infrequent	infrequent	1	only 1 since Aug 2012	none	0
EP13	27	>30	-	Normal	Unknown	Unknown	Unknown	infrequent	frequent	3	usually more than once a week but none since 6 weeks ago	LTG	1
EP14	57	<1	head injury 2001	Normal	Focal dyscog	Unknown	temporal	infrequent	infrequent	1	none since Sep 2012	None	0
EP15	22	<1	-	Normal	GTCS	Genetic	Generalised	infrequent	infrequent	2	2 since diagnosis	None	0
EP16	17	1	-	Normal (CT)	GTCS	Genetic	Generalised	infrequent	infrequent	1	single seizure	none	0
EP17	6 or 7 years old	30	-	Temporal lobe resection	Focal dyscog	Structural-metabolic	Temporal	infrequent	frequent	3	1 every ~2	CBZ/KEP	2
EP18	41	14	-	-	GTCS	Unknown	Temporal	infrequent	infrequent	2	1 every 6-8 weeks	none	0
EP19	3 years old	>20	VNS in situ- recent head injury-	Normal	Focal dyscog	Unknown	Possible frontal	frequent	frequent	4	every other night- approximately 12 per week	VPA- CLB- PER- PHT	4
EP20	1991	22	-	MRI- Normal	Focal motor	Unknown	Presumed left frontal	frequent	frequent	5	2-3 per day	RTG-CLB-CBZ-LEV	4
EP21	21	>30	cryptogenic focal epilepsy onset left frontotemporal region	Normal	Focal dyscog	Unknown	left frontotemporal	infrequent	frequent	3	2-3 per month	CBZ- LEV	2
EP22	2005	8	-	Normal	GTCS	Genetic	Generalised	infrequent	frequent	3	2 per month	LEV	1

ID	Age onset	Ep duration	PMH	Imaging	Seizure type	Presumed aetiology	Presumed location	Grading A	Grading B	GRADE	Detail of frequency	AED	Number of AEDs
EP23	13	30	Meningitis	L MTS	Focal dyscog	Structural-metabolic	Temporal	Frequent	Frequent	4	3 clusters per month or 9-10 per month	CBZ-ZNS	2
EP24	7	15	-	Normal	Tonic-clonic	Unknown	Presumed left occipital	Infrequent	Frequent	3	2-3 per month	TPM-ZNS	2
EP25	7	30	Tumour (pituitary macro adenoma)	L MTS	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Infrequent	2	Last one 29/08/13 before that 2 on 22/08/13 and before that January	ZNS	1
EP26	54	15	Depression	Normal	Focal dyscog	Unknown	Unknown	Infrequent	Infrequent	1	None in 2.5 years	VPA	1
EP27	58	10	-	Unknown	Bilateral convulsive	Unknown	Unknown	Infrequent	Infrequent	1	None since age 60	LTG	1
EP28	childhood	30	-	Normal	GTCS	Genetic	Generalised	Infrequent	Frequent	3	1 TC/Month every 6-7 days/month	VPA-LEV-CBZ	3
EP29	11-12	10	-	-	Generalised ; myoclonic	Genetic	Generalised	Frequent	Frequent	4	4/month sometimes several	ZNS	1
EP30	11-12	30	-	Unknown	-	Unknown	Unknown	Infrequent	Frequent	3	1/month	LEV- PER	2
EP31	28	20	Suspected meningitis as a child	R MTS	Focal dyscog	Structural-metabolic	Temporal	Frequent	Frequent	4	8 or 10/month in clusters	LTG-PGB	2
EP32	40	10	-	Normal	Focal dyscog	Unknown	Presumed temporal	Frequent	Frequent	4	2 to 4/week	LEV-RTG	2
EP33	around 51	30	Recent severe head injury	Normal	Focal dyscog	Unknown	Presumed temporal	Infrequent	Frequent	3	1/month	LTG	1

ID	Age onset	Ep duration	PMH	Imaging	Seizure type	Presumed aetiology	Presumed location	Grading A	Grading B	GRADE	Detail of frequency	AED	Number of AEDs
EP34	2000	13	-	Normal	Focal dyscog	Unknown	Presumed temporal	Frequent	Frequent	4	Refractory	PER-LEV-PGB	3
EP35	16	6	-	Normal	Focal dyscog	Unknown	Presumed temporal	Infrequent	Frequent	3	3-7 complex partial a month- last one 3/4/12	CBZ- TPM-CLB	3
EP36	2001	>30	Cerebral abscess	L parietal cortical resection in 2014- Hydrocephalous post operation	Focal dyscog	Structural-metabolic	Parietal	infrequent	infrequent	2	Every one to three months	PHT-LTG-LEV	3
EP37	23	4	PET: extensive right temporal lobe hypo metabolism	Normal	focal dyscog	Unknown	Presumed temporal	Frequent	Frequent	4	1 every other day- max 4-5/week	PER	1
EP38	1	>20	Tuberous sclerosis	Multiple tubers	Focal dyscog	Structural-metabolic	Multifocal	Frequent	Frequent	4	1/week	LEV- LTG-CLB	3
EP39	31	3	-	R MTS	Focal dyscog	Structural-metabolic	Temporal	Frequent	Frequent	5	0 to 5 a day	TPM-OXC-LTG	3
EP40	2014	<1	-	Normal	Primary generalised epilepsy	Genetic	Generalised	Frequent	Frequent	5	Daily or every other day	LEV	1
EP41	16	>10	-	Normal	Focal dyscog	Unknown	Presumed temporal	Frequent	Frequent	5	Minor seizures daily, major ones 1/week	CLB-LCM - LEV-ZNS	4
EP42	6	>20	sclerosis in the amygdala on right temporal lobe astrocytoma, partial resection 96, 97, right temporal lobectomy 99	Right mesial temporal sclerosis	Focal dyscog	Structural-metabolic	Temporal	Infrequent	Frequent	3	Clusters over 3-4 days and free seizures in between	LTG-PGB	2

ID	Age onset	Ep duration	PMH	Imaging	Seizure type	Presumed aetiology	Presumed location	Grading A	Grading B	GRADE	Detail of frequency	AED	Number of AEDs
EP43	14 or 15	>30	-	Normal	Bilateral convulsive with absence seizures	Genetic	Generalised	Infrequent	Infrequent	2	Estimate: 1-2 every 2 months	PRM - PGB	2
EP44	14	28-29	Head injury	MRI normal	absence and focal dyscog	Unknown	Presumed fronto-temporal	Frequent	Frequent	4	every 2-3 days	VPA-LTG	2
EP45	11	>20	Depression	Cystic encephalomalacia of right temporo-occipital	Focal dyscog and occasional tonic-clonic	Unknown	initial onset in frontal lobe with propagation to temporal lobe	Frequent	Frequent	4	More than 1 per week/ clusters	VPA- PGB-ESL-PB	4
EP46	~5	>25	-	Possible abnormality in left hippocampus	Nocturnal	Structural-metabolic	Left temporal lobe	Frequent	Frequent	4	More than 15 per month	PGB-LEV-CBZ- PHT-CLB	5
EP47	2009	~6	Head injury as a child	Small left hippocampal tail	Focal dyscog	Unknown	Presumed left anterior temporal	Frequent	Frequent	4	3 per week	ZNS, changed to CLB	1
EP48	1999	> 40	Asthma	left mesial temporal sclerosis	Focal dyscog	Structural-metabolic	Presumed temporal	Frequent	Frequent	4	More than 8 per week	CLB -VPA-CBZ	3
EP49	4-5	>25	-	Normal	Focal	Unknown	Presumed left temporal	Frequent	Frequent	4	once a week	OXC	1
EP50	22	~4	-	Normal	Possible focal dyscog	Unknown	Possible temporal lobe	Infrequent	Infrequent	2	used to have once or twice per week- now controlled	none	0
EP51	17-18	10	Encephalitis at ~10	Normal	Generalised seizures and focal dyscog	Structural-metabolic	Unknown	Infrequent	Infrequent	2	1 every 6 weeks/ but increased with start of the test	LTG, TPM	2
EP53	13-14	>10	-	Normal	Bilateral convulsive and absences	Unknown	Presumed frontal	Infrequent	Frequent	3	every 2 weeks	VPA- LEV	2

ID	Age onset	Ep duration	PMH	Imaging	Seizure type	Presumed aetiology	Presumed location	Grading A	Grading B	GRADE	Detail of frequency	AED	Number of AEDs
EP55	49-50	1-2	Ventricular tachycardia	Basal ganglia calcification	Focal dyscog	Unknown	Temporal lobe	Infrequent	Frequent	3	1-2 week	LEV	1
EP56	64	2006	-	Possible calcification or hemosiderin	Possible auto motor seizures	Unknown	Temporal lobe	Infrequent	Infrequent	2	2-3/month- now is decreased after increasing AED	LEV- it is decreasing to be replaced by ESL	1
EP57	9	>30	-	MRI normal	Simple partial seizures- occasional generalised tonic-clonic	Unknown	Right hemisphere	Infrequent	Infrequent	3	More than 1/month	ZNS- LEV- VPA	3

Appendix 3. Table of patients' information from India. Including patients ID, age of onset, type of seizure, date of last known seizure, details of seizure frequency, information regarding their grading and whether they belong to defined frequent and infrequent groups and their grade, anti-epileptic drugs (AEDs), the number of AEDs and presumed aetiology. The seizure classification is based on the old classification system.

ID	Age of onset	Type of seizure	date of last seizure	Seizure Frequency	Grading A	Grading B	Grade	AED	Number of AEDs	Presumed aetiology
KP1	59	Generalized Tonic Clonic Seizure	March 2011	23 times from 2009 to 2011	Infrequent	Infrequent	2	VPA - CLB	2	Genetic
KP2	16	Partial seizure	Jul-11	Once since 2011	Infrequent	Infrequent	1	VPA	1	Unknown
KP3	16	Generalized Tonic Clonic Seizure	11/09/2013	4 times per year	infrequent	infrequent	2	OXC, LEV	2	Genetic
KP4	11	Generalized Tonic Clonic Seizure	2011	2010-3 times, 2011-once	infrequent	infrequent	2	VPA	1	Genetic
KP5	14	Generalized Tonic Clonic Seizure, Absence seizure, myoclonic jerks	05/01/2013	3-4 times a year	infrequent	infrequent	2	LEV	1	Genetic
KP6	14	Complex Partial Seizure	19/11//2013	1-2 times per month	infrequent	frequent	3	LEV, VPA, CBZ	3	Unknown
KP7	16	Generalized Tonic Clonic Seizure	30/11/2013	5-6 times per week	frequent	frequent	4	VPA, LEV, CLB	3	Unknown
KP8	4	Complex partial seizure	Jul-13-2013	2-3 times a year	infrequent	infrequent	2	LEV	1	Unknown
KP9	17	Secondary seizures	Aug-13-2013	once in last 1 year	infrequent	infrequent	1	VPA	1	Structural/metabolic
KP10	18	Idiopathic Generalized epilepsy	Sep-13-2013	3-4 times a year	infrequent	infrequent	2	LEV	1	
KP11	5	Idiopathic Generalized epilepsy	Aug-12-2012	once in every month till 2012	infrequent	infrequent	2	VPA, PHT	2	Genetic
KP12	17	Secondary seizure Followed by Herpes Simplex Encephalitis	Oct-13-2013	4 times per year	infrequent	infrequent	2	OXC, CLB	2	Structural/metabolic
KP13	23	Complex Partial Seizure	Nov-13-2013	2 times a year	infrequent	infrequent	2	OXC	1	Unknown
KP14	54	Complex Partial Seizure	Dec-11-2011	7-8 times in a year from 2010-2011.	infrequent	infrequent	2	OXC, LEV	2	Unknown
KP15	26	Generalized Toni Clonic seizure	12/04/2013	2-3 times every day	frequent	frequent	5	VPA, CLB	2	Unknown
KP16	1	Complex Partial Seizure	12/04/2013	2-3 times every day	frequent	frequent	5	LEV, CBZ, CLB, LCM	4	Unknown

ID	Date of onset	Type of seizure	date of last seizure	Seizure Frequency	Grading A	Grading B	Grade	AED	Number of AEDs	Presumed aetiology
KP17	14	Partial seizure with secondary generalised	2012	once in every month till 2012	infrequent	infrequent	2	OXC, LEV	2	Structural/metabolic
KP18	35	Partial seizure	2012	once in 4 months till 2012	infrequent	infrequent	2	OXC	1	Unknown
KP19	16	complex Partial Seizure with secondary generalization	Nov-13-2013	4 times per year	infrequent	infrequent	2	LEV	1	Unknown
KP20	22	Generalized Epilepsy	Nov-13-2013	5 times in one year	infrequent	infrequent	2	LEV	1	Unknown
KP21	15	Complex Partial Seizure	Aug-13-2013	once in a year	infrequent	infrequent	1	OXC	1	Unknown
KP22	16	Complex Partial Seizure	12/05/2013	5/6 times a month	frequent	frequent	4	OXC, CLB	2	Unknown
KP23	26	Idiopathic Generalized epilepsy	30/11/2013	missing	missing	missing	missing	LEV, CLB	2	Genetic
KP24	55	Partial seizure with secondary generalization	2011	once in a year	infrequent	infrequent	1	LEV	1	Unknown
KP25	3	Partial seizure with secondary generalization	12/06/2013	1-2 times per week	frequent	frequent	4	LEV, OXC, VPA, CLB	4	Unknown
KP26	19	Idiopathic Generalized epilepsy	Oct-13-2013	3-4 times a year	infrequent	infrequent	2	OXC, CLB	2	Genetic
KP27	19	Idiopathic Generalized epilepsy	Feb-13-2013	once in a year	infrequent	infrequent	1	LEV	1	Genetic
KP28	40	Generalized Tonic Clonic seizure	Sep-12-2012	once since 2012	infrequent	infrequent	1	VPA	1	Unknown
KP29	55	Idiopathic Generalized epilepsy	13/12/2012	1/2 times a month	infrequent	frequent	3	VPA, OXC, LEV	3	Genetic
KP30	4	Complex Partial Seizure	12/12/2013	3/4 times a year	infrequent	infrequent	2	Missing	Missing	Unknown
KP31	18	Generalized Tonic Clonic Seizure	22/11/2013	Twice on the first day, no attack after that	infrequent	infrequent	1	PHT, CLB	2	Unknown
KP32	35	Generalized Tonic Clonic Seizure	Jul-13-2013	4 times in last one year	infrequent	infrequent	2	VPA PB	2	Unknown
KP33	15	Complex Partial Seizure	31/12/2013	5-6 times in last 0ne year	infrequent	infrequent	2	LEV, CBZ, CLB	3	Unknown
KP34	1	Generalized Tonic Clonic Seizure	April,2014	2-3 times every month	infrequent	frequent	3	OXC, LEV, CLB	3	Unknown
KP35	31	Generalized Tonic Clonic Seizure	February ,2012	total 2 episodes so far	infrequent	infrequent	2	VPA, CLB	2	Unknown
KP36	25	Generalized Tonic Clonic Seizure	03/11/2013	2 seizures only	infrequent	infrequent	2	OXC	1	Unknown

ID	Date of onset	Type of seizure	date of last seizure	Seizure Frequency	Grading A	Grading B	Grade	AED	Number of AEDs	Presumed aetiology
KP37	60	Generalized Tonic Clonic Seizure	ONE episode so far	Single seizure	infrequent	infrequent	1	VPA, LEV, CLB	3	Unknown
KP38	29	Generalized Tonic Clonic Seizure	Mar-14-2014	3 episodes in last three year	infrequent	infrequent	1	OXC	1	Unknown
KP39	16	Partial seizure with secondary generalization	15/05/2014	1-2 episodes per month	infrequent	frequent	3	OXC, VPA	2	Unknown
KP40	23	Lt Focal motor seizure with secondary generalization	Jun-14-2014	2 episodes in last 1 year	infrequent	infrequent	2	PHT, OXC , CLB	3	Unknown
KP41	12	Juvenile Myoclonic Epilepsy	14/01/2011	No Episode in the last 3 years	infrequent	infrequent	1	VPA	1	Genetic
KP42	24	Generalized Tonic Clonic Seizure	20/04/2014	1-2 ties every month	infrequent	frequent	3	CBZ, VPA	2	Unknown
KP43	57	Post head injury GTCS	17/05/2014	once in two month	infrequent	infrequent	2	PHT, CLB	2	Structural/metabolic
KP44	52	Post Stroke seizure	February ,2014	2 attacks in last one year	infrequent	infrequent	2	none	0	Structural/metabolic
KP45	29	Generalized Tonic Clonic Seizure	Mar-14-2014	once in two month	infrequent	infrequent	2	PHT, , LTG, CLB	3	Unknown
KP46	11	Generalized Tonic Clonic Seizure	Jan-13-2013	once in six month	infrequent	infrequent	2	LEV, OXC	2	Unknown
KP47	58	Post Stroke seizure	April,2014	Once in last one year	infrequent	infrequent	1	PHT	1	Structural/metabolic
KP48	27	Complex Partial Seizure	April,2014	Once in a week	frequent	frequent	4	CBZ, CLB	2	Unknown
KP49	Since birth	Idiopathic Generalized Epilepsy	3 years ago	missing info	missing	missing	missing info	VPA	1	Genetic
KP50	21	Generalized Tonic Clonic Seizure	20/5/2014	5 times in last 15 days	frequent	frequent	4	OXC, CLB	2	Unknown
KP51	21	Generalized Tonic Clonic Seizure	22/5/2014	4 episodes so far (in 2 months)	frequent	frequent	4	OXC	1	Unknown
KP52	9	Generalized Tonic Clonic Seizure	17th may 2014	2-3 times every month	infrequent	frequent	3	LEV, VPA, OXC, ZNS, CLB	4	Unknown
KP53	16	Occipital Lobe seizure	Dec-12	4 attacks in 4 months	infrequent	frequent	3	OXC	1	Unknown
KP54	29	Complex Partial Seizure	27/05/204	Once in a week	frequent	frequent	4	OXC, LEV, LCM, CLB	4	Unknown
KP55	12	Juvenile Myoclonic Epilepsy	3 weeks age	2 attacks in last 3 months	infrequent	infrequent	2	VPA	1	Genetic

ID	Date of onset	Type of seizure	date of last seizure	Seizure Frequency	Grading A	Grading B	Grade	AED	Number of AEDs	Presumed aetiology
KP56	19	Juvenile Myoclonic Epilepsy	two weeks ago	once in a month	infrequent	frequent	3	VPA	1	Genetic
KP57	17	Generalized Tonic Clonic Seizure	Oct-13-2013	>20 attacks in 2013 , No attack in 2014 so far	infrequent	infrequent	2	VPA, LCM	2	Unknown
KP58	6	Absence Seizure	May-14-2014	one-two attacks/ month	infrequent	frequent	3	OXC, LEV	2	Genetic
KP59	12	Generalized Tonic Clonic Seizure	2010	missing info	missing	missing	missing info	CBZ	1	Unknown
KP60	20	Generalized Tonic Clonic Seizure	27/05/2014	4 attacks in last 1 year	infrequent	infrequent	2	LEV, CLB	2	Unknown

Appendix 4. Patients' information sheet

Version 1.3 February 2013

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University
The Institute of Neuroscience

Assessing seizure susceptibility using psychophysical tests

Patient Information Sheet

You are being invited to take part in a research study. Before you accept or decline the invitation, it is important for you for to understand why the research is being done and what it will involve. Please read the following information and discuss it with relatives, friends and your GP, if you wish. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 2). Take time to decide whether you would like to take part, or not.

You are being invited to take part in this research because you had a seizure, and we are trying to get more information on patients, like you, with similar conditions.

The aim of this research is to see whether it is possible to predict what risk someone has of suffering a seizure. Recent work suggests that certain classes of cells in the brain (neurons) are particularly important in protecting us against seizures. Consequently, problems with these neurons may cause seizures. Intriguingly, these same neurons also perform other functions in the brain, for example sensory processing. If so, then one may be able to monitor a person's seizure risk using simple tests of sensory perception known as psychophysical tests.

Before you consider taking part, it is important that you understand what is involved and what will be done during the study. At the end of the form, and after you have had some time to think about it, we will ask if you wish to take part. If you do, we will ask you to sign a consent form saying that you agree to join. If you have any questions please contact us before signing the consent form (contact details on page 2).

"What do the tests involve?"

You will be asked to attend the Department of Clinical Neurophysiology at the Royal Victoria Infirmary, Newcastle upon Tyne. This will be at a time of your choosing. There, you will be given the opportunity to discuss the project with a member of the research team, and if you decide to go ahead, you will be asked to sign a consent form.

You will then be taken to a clinical room within the department and asked to relax in a comfortable chair. We will then assess your memory using a questionnaire.

You will then be asked to look at a series of images on a computer screen, and to listen to sounds played over a pair of headphones. You will be asked to press a button when you have seen an image or heard a sound. This takes about 30 minutes.

Ideally we would like you to do the tests every few months so that we can see whether your responses change with time. This could be in the Royal Victoria Infirmary, and again would be at a time of your choosing. Alternatively, we are also developing a home-testing system. This consists of a laptop or tablet computer, which displays the same images as the system used in the hospital. If you are selected for this aspect of the study, we will ask you to take this home with you to perform the tests yourself. We will ask you to perform the tests once a week for six months and to record whether you have any seizures during this period in a diary. We will then ask you to bring the home-testing system back to the hospital with the diary so that we can analyse the data.

"Are the tests safe?"
Yes, the stimuli have been carefully chosen so as to present no obvious risk.

"How will I benefit from taking part?"
Our ultimate aim is to improve the care of patients with conditions similar to yours. However, any benefits as a result of this trial are likely to take many years to develop, and may not apply to you personally. You will not benefit directly from taking part in the study. You will not receive any payment or any other financial benefit as a result of joining the study, other than travel expenses. The results of research arising from the study may have business potential, but you will not receive financial benefits from such development.

"Will information about me be kept confidential?"
All information we receive from you will be treated confidentially. Details of your specific diagnosis as well as personal information (name, age, address, gender) will be stored on a secure computer within the Newcastle Hospital NHS Foundation Trust. This information is all required to enable us to match you with control subjects, and to allow us to contact you at the end of the study with a summary of the results (should you wish). Only members of Dr Whittaker's team given specific permission by him will be allowed to look at this information. The information gathered during the tests will be converted into code, anonymised, and stored on a secure computer located at Newcastle University. This data will be analysed by members of the research team based in Newcastle University, but they will have no access to any personal information about you. If we publish any research or other documents based on information from the study, this will not identify you by name.

"Do I have to join the study and can I withdraw if I change my mind?"
Joining the study is voluntary. Should you wish to withdraw your information from the study you will be free to do so at any time without having to provide any explanation. If you wish to withdraw, you should get in touch with the staff in charge of the study. Contact details are provided below. Joining or leaving the study will in no way affect the care you receive for your condition.

"Who has reviewed this project?"
All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your data in this project.
This research has been reviewed by Newcastle and North Tyneside 1 Research Ethics Committee who have decided they are happy for us to go ahead with the study.

"What do I do now if I want to take part in the study?"
If you are interested in taking part in this study, please contact the principal investigator:

Dr Roger G Whittaker; Tel: (0191) 2824578; email; roger.whittaker@nuth.nhs.uk

Researcher:

Partow Yazdani
Tel: 07432644091; email: p.yazdani@ncl.ac.uk

Thank you for taking the time to read this information sheet.

Appendix 5. The Addenbrooke's cognitive examination (ACE-R) (Mioshi et al., 2006).

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

Name :
Date of birth :
Hospital no. :

Addressograph

Date of testing:..... /...../.....
Tester's name: .....
Age at leaving full-time education: .....
Occupation: .....
Handedness: .....

ORIENTATION

➤ Ask: What is the	Day	Date	Month	Year	Season	[Score 0-5]
➤ Ask: Which	Building	Floor	Town	County	Country	[Score 0-5]

REGISTRATION

➤ Tell: 'I'm going to give you three words and i'd like you to repeat after me: lemon, key and ball'. After subject repeats, say 'Try to remember them because i'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).

Register number of trials .....

[Score 0-3]

ATTENTION & CONCENTRATION

➤ Ask the subject: ' could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 84, 77, 70, 63 -score 4)

Stop after five subtractions (93, 86, 79, 72, 65). ....

➤ Ask: 'could you please spell **WORLD** for me? Then ask him/her to spell it backwards:

....

[Score 0-5] (for the best performed task)

MEMORY - Recall

➤ Ask: 'Which 3 words did I ask you to repeat and remember?'

....

[Score 0-3]

MEMORY - Anterograde Memory

➤ Tell: ' I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times, so you have a chance to learn it. I'll be asking you later'

Score only the third trial

[Score 0-7]

	1st Trial	2nd Trial	3rd Trial
Harry Barnes	....	....	....
73 Orchard Close	....	....	....
Kingsbridge	.....	.....	.....
Devon	.....	.....	.....

MEMORY - Retrograde Memory

[Score 0 -4]

➤ Name of current Prime Minister .....
➤ Name of the woman who was Prime Minister .....
➤ Name of the USA president .....
➤ Name of the USA president who was assassinated in the 1960's .....

ATTENTION&ORIENTATION MEMORY

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VERBAL FLUENCY - Letter 'P' and animals

➤ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P'

[Score 0 - 7] ☐

>17	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
<2	0
total	correct

➤ **Animals**

Say: 'Now can you name as many animals as possible, beginning with any letter?

[Score 0 - 7] ☐

>21	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
total	correct

FLUENCY

LANGUAGE - Comprehension

➤ Show written instruction: [Score 0-1] ☐ ☐

Close your eyes

➤ 3 stage command:
'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor'

[Score 0-3] ☐ ☐

LANGUAGE - Writing

➤ Ask the subject to make up a sentence and write it in the space below:
Score 1 if sentence contains a subject and a verb (see guide for examples)

[Score 0-1] ☐ ☐

LANGUAGE

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LANGUAGE - Repetition

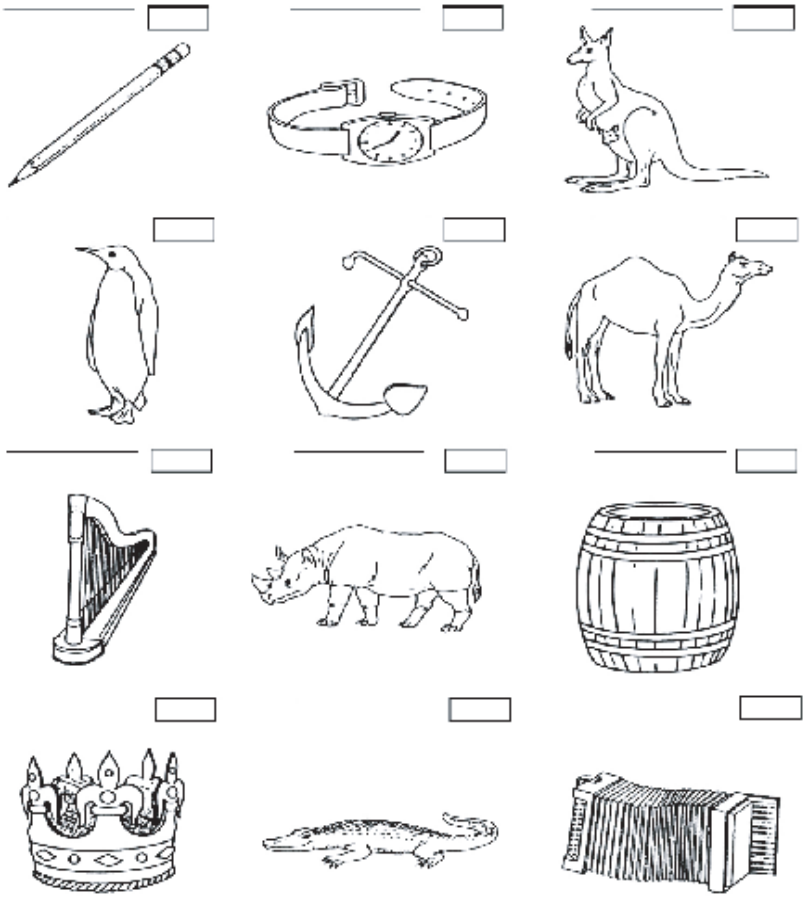
➤ Ask the subject to repeat:' **hippopotamus'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all correct; 1 if 3 correct; 0 if 2 or less. [Score 0-2]

➤ Ask the subject to repeat: **'Above, beyond and below'** [Score 0-1]

➤ Ask the subject to repeat: **'No ifs, ands or buts'** [Score 0-1]

LANGUAGE - Naming

➤ Ask the subject to name the following pictures: [Score 0-2] pencil + watch



[Score 0-10]

LANGUAGE - Comprehension

➤ Using the pictures above, ask the subject to: [Score 0-4]

- Point to the one which is associated with the monarchy _____
- Point to the one which is a marsupial _____
- Point to the one which is found in the Antarctic _____
- Point to the one which has a nautical connection _____

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LANGUAGE

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R *Final Revised Version (2006)*

LANGUAGE - Reading

➤ Ask the subject to read the following words: [Score 1 only if all correct] [Score 0-1]

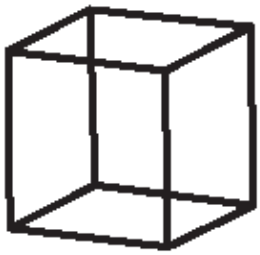
sew
pint
soot
dough
height

LANGUAGE

VISUOSPATIAL ABILITIES

➤ Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1]

➤ Wire cube : Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2]



➤ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5]

VISUOSPATIAL

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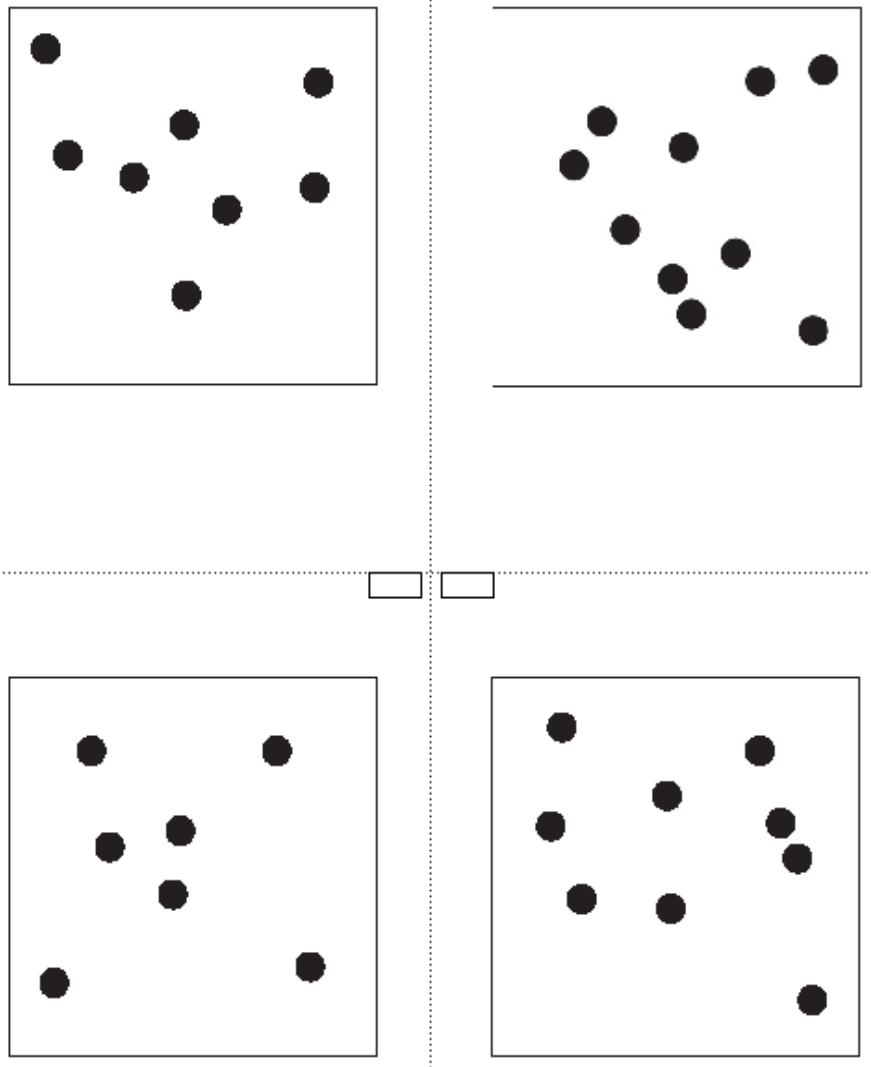
PERCEPTUAL ABILITIES

➢ Ask the subject to count the dots without pointing them

[Score 0-4]



VISUOSPATIAL

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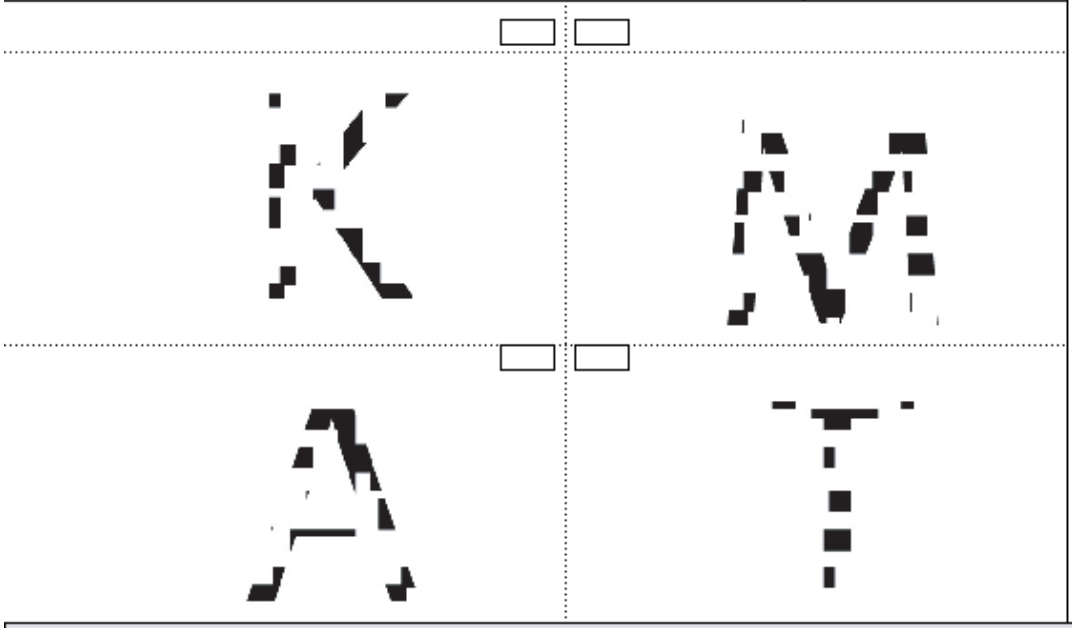
ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2006)

PERCEPTUAL ABILITIES

➢ Ask the subject to identify the letters

[Score 0-4]



V I S U O S P A T I A L

RECALL

➢ Ask "Now tell me what you remember of that name and address we were repeating at the beginning"

[Score 0-7]

Harry	Barnes	....
73 Orchard	Close	....
Kingsbridge		.....
Devon		.....

RECOGNITION

➢ This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right hand side. Then test not recalled items by telling "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point which is added to the point gained by recalling.

[Score 0-5]

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

M E M O R Y

General Scores

MMSE	/30
ACE-R	/100

Subscores

Attention and Orientation	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

S C O R E

Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86

Cut-off <88 gives 94% senstivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

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Appendix 6. Patient information sheet regarding seizures

Subject ID _____

Date of study _____

VA R_____ L_____

ACE _____

Age at first seizure _____

Current seizure type _____

_____

_____

Current seizure frequency _____

Current AEDS _____

Comments

Healthy participant information:

Appendix 7. Control information sheet

Version 1.4 February 2013

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University
The Institute of Neuroscience

Assessing seizure susceptibility using psychophysical tests

Control Subject Information Sheet

You are being invited to take part in a research study. Before you accept or decline the invitation, it is important for you for to understand why the research is being done and what it will involve. Please read the following information and discuss it with relatives, friends and your GP, if you wish. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 2). Take time to decide whether you would like to take part, or not.

The aim of this research is to see whether it is possible to predict what risk someone has of suffering an epileptic seizure. Recent work suggests that certain classes of cells in the brain (neurons) are particularly important in protecting us against seizures. Consequently, problems with these neurons may cause epilepsy. Intriguingly, these same neurons also perform other functions in the brain, for example sensory processing. If so, then one may be able to monitor a person's seizure risk using simple tests of sensory perception known as psychophysical tests.

Our hope is that ultimately, we may tailor medication to individual patients, guided by assessment of their sensory pathways. For instance, we might recognize increasing seizure risk even before patients develop epilepsy, and start a person on a low dose of an antiepileptic drug to delay or even prevent that first seizure.

Before you consider taking part, it is important that you understand what is involved and what will be done during the study. At the end of the form, and after you have had some time to think about it, we will ask if you wish to take part. If you do, we will ask you to sign a consent form saying that you agree to join. If you have any questions please contact us before signing the consent form (contact details on page 2).

"What do the tests involve?"

You will be asked to attend the Department of Clinical Neurophysiology at the Royal Victoria Infirmary, Newcastle upon Tyne. This will be at a time of your choosing. There, you will be given the opportunity to discuss the project with a member of the research team, and if you decide to go ahead, you will be asked to sign a consent form.

You will then be taken to a clinical room within the department and asked to relax in a comfortable chair. We will then assess your memory using a questionnaire.

You will then be asked to look at a series of images on a computer screen, and to listen to sounds played over a pair of headphones. You will be asked to press a button when you have seen an image or heard a sound. This takes about 30 minutes.

"Are the tests safe?"
Yes, the stimuli have been carefully chosen so as to present no obvious risk.

"How will I benefit from taking part?"
You will be paid £10 pounds to take part in this study to cover your expenses. Our

ultimate aim is to improve the care of patients with certain forms of epilepsy. However, any benefits as a result of this trial are likely to take many years to develop. You will not benefit directly from taking part in the study. You will not receive any payment or any other financial benefit as a result of joining the study, other than travel expenses. The results of research arising from the study may have business potential, but you will not receive financial benefits from such development.

"Will information about me be kept confidential?"
All information we receive from you will be treated confidentially. Details of your personal information (name, age, address, gender) will be stored on a secure computer within the Newcastle Hospital NHS Foundation Trust. This information is all required to enable us to match you with the patients being studied, and to contact you at the end of the study if you would like to receive a summary of the results. Only members of Dr Whittaker's team given specific permission by him will be allowed to look at this information. The information gathered during the tests will be converted into code, anonymised, and stored on a secure computer located at Newcastle University. This data will be analysed by members of the research team based in Newcastle University, but they will have no access to any personal information about you. If we publish any research or other documents based on information from the study, this will not identify you by name.

"Do I have to join the study and can I withdraw if I change my mind?"
Joining the study is voluntary. Should you wish to withdraw your information from the study you will be free to do so at any time without having to provide any explanation. If you wish to withdraw, you should get in touch with the staff in charge of the study. Contact details are provided below.

"Who has reviewed this project?"
All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your data in this project.
This research has been reviewed by the Newcastle and North Tyneside Research Ethics Committee who have decided they are happy for us to go ahead with the study.

"What do I do now if I want to take part in the study?"
If you are interested in taking part in this study, please contact the principal investigator:

Dr Roger G Whittaker; Tel: (0191) 2824578; email; roger.whittaker@nuth.nhs.uk

Thank you for taking the time to read this information sheet.

Appendix 8. Consent from for control participants.

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

The Institute of Neuroscience

REC no: 09/H0906/90

CONSENT FORM for controls

Title of Study:

Assessing seizure susceptibility using psychophysical tests

Name of Researcher:
Dr Roger G Whittaker
Consultant Clinical Neurophysiologist,
Department of Clinical Neurophysiology,
Royal Victoria Infirmary,
Queen Victoria Road,
Newcastle upon Tyne,
NE1 4LP.

Please write your initials in the box

1. I confirm that I have read and understand the information sheet dated February 2013 (version 1.4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. By signing this document, I understand that I give consent for the research team to perform tests which assess the function of my visual and auditory systems. ☐

4. I understand that the anonymised results of these tests will be passed to researchers in Newcastle University for analysis. ☐

5. I understand that the results from this or from future research may not have any direct benefits for myself or my family. ☐

6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

_____	_____	_____
Name of subject	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

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