The effects of task-induced stress and mental workload on visual performance and eye movement behaviour in nystagmus and controls.

Marzieh Salehi Fadardi

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Department of Optometry and Vision Sciences
The University of Melbourne, Australia

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**Declaration**

This is to certify that:

i. the thesis comprises only my original work towards the PhD except where indicated in the text,

ii. due acknowledgement has been made in the text to all other material used,

iii. the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

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Marzieh Salehi Fadardi

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Abstract

Background and aims

During daily activities, individuals may experience stress when a visual task is combined with an irrelevant mental task (e.g. conversing). Clinical examinations of patients with infantile nystagmus syndrome (INS) may elicit subjective reports of worsened nystagmus under internal states such as stress. Although the negative effects of stress on visual function have been widely studied in healthy subjects, few studies are available for patients with INS. Previous findings have demonstrated that INS is influenced by task conditions (i.e. visual demand and internal states such as stress); however, these studies limited their methodologies to only the null or central gaze position. Gaze position, solely, can affect visual function in INS and can affect INS parameters such as foveation time. By acknowledging that gaze position can affect INS, one gaze position (e.g. central) may not be enough to measure the changes in INS arising from task variations. Here, we hypothesised that a task-induced change from baseline in INS parameters at the null position would differ from task-induced changes at the gaze position away from the null.

Patients with INS may also complain of being slow to see. Target acquisition time and the following visual processing time can affect the total period taken to react to a visual object. Surgical improvement in foveation has resulted in a reduction in both target acquisition time and visual recognition time. A few studies have reported that stress exacerbates nystagmus by increasing its intensity and reducing foveation time. Since tenotomy has been reported to decrease target acquisition time in INS, there was a possibility that changes in INS parameters under internal states such as stress affected target acquisition time. Thus, our second hypothesis stated that the effects of stress on visual timing would differ between control and INS subjects. The objective was to measure the extent to which saccades, target acquisition and visual processing times are affected by cognitively induced stress in INS subjects in comparison to the control group.
Methods

To test our first hypothesis, we conducted a visual acuity experiment. We varied task conditions by manipulating levels of mental load and visual demand, thus inducing varying stress levels. Participants with idiopathic INS were required to determine the direction of Tumbling-E targets, which varied in size and contrast, using a staircase procedure across ±25° gaze positions, with 5° steps from the centre.

To test our second hypothesis, we conducted a saccade experiment, which required INS and control subjects to respond to the direction of horizontal E targets presented randomly at the post-saccade position, set at ±25° with 5° step, away from the centre. Visual task performance was measured by subjects’ reaction time and their response accuracy to the direction of the post-saccade target.

Each of the above tasks was performed under two conditions: alone (low mental load) and with mental arithmetic and time restriction (induced high mental load). Perceived workload across these task conditions was assessed via changes in heart rate as well as other physiological measurements such as skin conductance level, and subjective ratings. The subjects’ eye movements and visual task performance were recorded across varying task conditions.

Results

The induction of the mental arithmetic task and time restriction increased mental workload. For both visual acuity and saccade experiments, the metrics of task performance worsened under high mental load.

For the visual acuity experiment, there was a significant interaction between mental load and gaze position for foveation time and task performance. Interaction effects were interpreted as follows; during high visual demand, the change in foveation time due to mental load was greater at the null than away from it. Similarly, the increase in last optotype size from the low to high mental load condition was more pronounced at the null than away from it.
During both low and high mental load, saccade latency, target acquisition time, and visual recognition time were longer in the INS group in comparison to controls. For both control and INS subjects, saccade latency and target acquisition time increased with high mental load. The LATER model (Linear Approach to Threshold with Ergodic Rate), implemented to analyse saccade latency in the control group, highlighted that the rate of rise in saccade decision signal decreased during high mental load. Visual recognition time increased with high mental load only in the INS group. The effects of mental load on the gain of prosaccades and target acquisition time varied between INS and control subjects.

Discussion

We suggested that the extent to which foveation duration contributes to visual function varies across both task conditions and gaze positions. We agreed with the notion that an extended foveation time does not guarantee an improvement in visual task performance in INS. Previous studies have highlighted that INS subjects are late in detecting a new target, which can result in a delay in target acquisition. Consistent with the literature, our study concluded that difficulty in the accurate programming of eye movements used to acquire a new target can also delay target acquisition time.

Our results suggest that a further increase in target acquisition time with stress worsens the phenomenon of being slow to see in INS. We concluded that an increase in saccade latency with high mental load is due to a reduction in the capacity of information processing resources in both individuals with and without INS. However, visual recognition time in INS is multifactorial and can show additional increases under stress (e.g. driving) when compared to normal subjects. We have suggested that the efficacy of visual processing further decreases with effort to see in INS.

Conclusion

Possible main and interaction effects of task condition and gaze position on foveation time can lead to an overestimation of visual function in INS. Accuracy and speed of the subjects’ response to visual targets should be measured with a mental load resembling real world conditions. The results can be useful in relation to work safety and clinical assessment of INS, especially in terms of treatment outcomes.
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Lists of abbreviations

- ACC (anterior cingulate cortex)
- ANOVA (analysis of variance)
- AP (asymmetric pendular)
- APAN (aperiodic alternating nystagmus)
- BDJ (bidirectional jerk)
- bpm (beats per minute)
- BVP (blood volume pulse)
- CI (confidence interval)
- DJ (dual jerk nystagmus waveform)
- DLPFC (dorsolateral prefrontal cortex)
- FEF (frontal eye fields)
- FMNS (fusion maldevelopment nystagmus syndrome)
- fMRI (functional magnetic resonance imaging)
- FP (foveation period, foveation time)
- HR (heart rate); HRV (heart rate variability)
- HV5 (five horizontal and vertical fixation points)
- HV9 (nine horizontal and vertical fixation points)
- INS (infantile nystagmus syndrome)
- J (jerk nystagmus waveform)
- Jef (jerk with extended foveation nystagmus waveform)
- JL (jerk left)
- JR (jerk right)
- L (left eye)
- LATER (linear approach to threshold with ergodic rate)
- LIP (lateral intraparietal area)
- LogMAR (logarithm of minimum angle of resolution)
- Ls (latency of saccades)
- Lt (target acquisition time)
- MTE (mental, temporal and effort subscales)
- NAFX (expanded nystagmus acuity function)
- NASA-TLX (National Aeronautics and Space Administration Task Load Index)
- nparLD (Nonparametric Analysis of Longitudinal Data in Factorial Experiments)
- P300 (event-related potential waveform)
- PAN (periodic alternating nystagmus)
- PC: (pseudocycloid nystagmus waveform)
- Pfs (Pendular with foveating saccades)
- PMN (pre-motor negativity)
- PMP (pre-motor positivity potential)
- PPfs (pseudopendular with foveating saccades)
- PPRF (paramedian pontine reticular formation)
- R (right eye)
- riMLF (rostral interstitial nucleus of the medial longitudinal fasciculus)
- RT (manual response time, reaction time in manual task)
- SC (superior colliculus)
- SCL (skin conductance level)
• SD (standard deviation)
• SEF (supplementary eye fields)
• SEM (standard error of mean)
• Tc (stimulus time within nystagmus cycle)
• Tc% (normalised stimulus time within nystagmus cycle)
To my son on his 4th birthday
Chapter one: Introduction

Workload has been defined as the mental exertion and physical preparation to protect performance from disruption (Roscoe, 1992). Effort is applied only if it can improve performance (Adams, Tenney & Pew, 1991). Workload is more accurately measured by a multidimensional measurement test rather than a single one (Ryu & Myung, 2005), therefore this thesis has used multidimensional measurement to identify induced workload. Since physical aspects of the tasks discussed in this thesis are minor, e.g. pressing a button with the finger, the term ‘workload’ used in this thesis refers to the mental workload, which is induced by cognitive aspects of the tasks rather than their physical demands. The term task-induced stress has been previously used in the nystagmus literature to describe the mental workload induced by concurrently performing both visual discrimination and mental arithmetic tasks, that is, visual and mental demands (Cham, Anderson and Abel, 2008a-b). Chapter 2, section 1.1 explain the term mental workload, which is used as the basis for the experimental design in this thesis, in more detail.

Infantile nystagmus syndrome (INS) has been defined as involuntary oscillatory eye movements presenting at birth, shortly after, or rarely in later life (Dell'Osso & Daroff, 1975; Gresty, Bronstein, Page & Rudge, 1991). It is common knowledge that psychological factors such as stress, tiredness, fixation attempt, and effort to see target details can worsen INS (Abadi & Dickinson, 1986; Abadi & Bjerre, 2002). Cham et al. (2008b) for the first time showed INS parameters deteriorated through stress resulting from a high cognitive load during a visually demanding task. In other words, foveation reduced and INS intensity increased. However, that study examined only the central gaze position. Visual acuity and nystagmus intensity are gaze dependent in nystagmus subjects (Hertle et al., 2003). Although INS parameters can be influenced by gaze position and task condition (Abadi & Bjerre, 2002; Wiggins, Woodhouse, Margrain, Harris & Erichsen, 2007; Cham et al., 2008b; Jones et al., 2013), there are still no data available to demonstrate the effect different gaze positions have on nystagmus in the presence of internal factors such as increased cognitive load. Time restriction has been shown to reduce visual acuity in INS, and that reduction varied across gaze positions (Yang, Hertle, Hill &
Stevens, 2005). Whereas the nystagmus waveform typically appears to allow for the best vision at the null (Gresty, Page & Barratt, 1984; Hertle & Dell'Osso, 2013b), there is a possibility that the effects of increased mental load on INS could vary with gaze, as there is more scope for deterioration at the null than at some distance away from it. Here, we hypothesised that a task-induced change from baseline in INS parameters at the null position would differ from task-induced changes at other gaze positions.

Longer latency of eye movements such as saccade execution and late target acquisition has been found in patients with nystagmus as compared to controls (Wang & Dell'Osso, 2007a). It has been suggested that longer target acquisition time markedly contributes to the complaint of being “slow to see” in patients with INS (Wang & Dell'Osso, 2007a; Dunn, Margrain, Woodhouse & Erichsen, 2015). Post-tenotomy measures of INS have shown both an increase in foveation duration and a decrease in target acquisition time (Wang & Dell’Osso, 2008). Whereas changes in foveation due to tenotomy can have an effect on target acquisition time, it may also be possible that changes in foveation due to task conditions, such as visual demand level and internal states, have an effect on target acquisition time in patients with INS. However, the effects of task condition such as mental stress on target acquisition time have not yet been investigated in INS.

Dunn et al. (2015) found that the time taken to process visual information was similar between normal controls and INS patients. However, the visual demand level of the post-saccadic target was low and the experiment was not designed to compare task conditions. It has been suggested that patients with INS can see target details through temporal summation of foveation durations, or total exposure time (Jones et al., 2013). Task demands and internal states have been reported to have an effect on both foveation and INS frequency (Cham et al., 2008b; Jones et al., 2013). Changes in foveation duration and INS frequency due to task conditions may influence how fast a patient with INS can recognize target details after it appears at a new location. However, possible effects of task conditions on saccade task parameters; e.g., latency, gain, target acquisition time, and visual processing time in INS have not yet been investigated.

Both target localisation and resolving target details may be necessary during a cognitively demanding task. An assessment of subjects’ response times to visual targets and eye movement reaction times with different levels of task difficulty, and at different gaze angles, may help us to
better understand how nystagmus may change under different situations in daily life. To accomplish this, the current project aims to investigate eye movements and subjects’ response times during visually demanding tasks, in the absence and presence of a high mental load, in both normal and nystagmus subjects. Eye movements will be recorded during visually demanding tasks at different gaze positions using a visual discrimination task (first experiment) and a demanding saccadic task (second experiment) in the absence and presence of a high mental load.

Nystagmus subjects can experience mental stress in daily life. The findings of this study will help to better evaluate nystagmus under conditions more closely resembling the real world, in which stress may occur when both refixation of an object and resolving its details are required. The results will help for future nystagmus modeling and to better understand how nystagmus changes with internal states.
Chapter two: Literature review

In this chapter, nystagmus and its common forms are reviewed. The main concepts of this thesis, including the infantile form of nystagmus, and cognitive and mental load will be explained. This chapter discusses available metrics to evaluate mental load and visual function in nystagmus. The impacts of visual demand and high mental load found in previous studies will be reviewed for both people with normal eye and vision health condition (normal subjects), and those with nystagmus. The gaps in previous findings, and their importance, will be specifically explained later at end of this chapter.

1. Mental workload

1.1. Definition

Mental workload has been defined in relation to effort, when a person is working harder and expending more energy to meet task demands. It refers to the degree of information processing capacity that is allocated during task performance (Eggemeier, 1988). Stress is related to inefficient behavior, negative emotions, and ineffective energy spent for task performance and can be induced under psychological states; e.g. subjects’ emotions of arousal and frustration. In contrast with stress, workload is the energy spent to cover task demands. Although sustained high workload may elicit stress, workload itself is not critical to producing stress (Gaillard, 1993). The term, “task-induced stress” is used by some nystagmus investigators (Cham et al., 2008a-b), and includes the above explanation that this thesis uses to define increased mental workload, i.e. spending more energy and trying harder to cover task demands.

1.2. Metrics

The level of mental workload can be assessed using different metrics, such as subjective tests and task performance, including accuracy and response time. The amount of energy spent to do the task can also be evaluated objectively by means of physiological measurements (Backs & Seljos, 1994; Meshkati, Hancock, Rahimi & Dawes, 1995; Weinger et al., 2000; Fairclough & Houston, 2004).
Changes in cognitive strategy and higher efficiency of mental capacity, i.e. less additional energy needed to accomplish a task, have been used to explain physiological differences between good and poor performers (Haier et al., 1992; Backs & Seljos, 1994). It has been explained that “skill-based behavior” is controlled through “well-learned procedures” of the supervisory cortical system and needs little effort to maintain task performance. In contrast, a high workload that needs active, attention-demanding control and real-time processing is associated with higher mental effort and physiological changes (Tattersall & Hockey, 1995).

Although physiological measurements seem to be more reliable than subjective tests (Haga, Shinoda & Kokubun, 2002), other factors besides mental workload, such as respiration and physiological diseases, can have an effect on physiological results (Veltman & Gaillard, 1998). Their ease of use, low cost, high validity, and sensitivity have made subjective workload tests more popular (Hendy, Hamilton & Landry, 1993; Luximon & Goonetilleke, 2001).

Usually at a higher level of task difficulty, response time and error rates increase while a shorter reaction time is related to the amount of attention allocated towards the stimulus and the subject’s ability to apply sustained attention (Fleck, Sax & Strakowski, 2001; Karatekin, 2004; Silk et al., 2009). However, a higher workload does not necessarily worsen task performance, and both high and low performances have been reported at low levels of workload (Backs & Seljos, 1994; Ryu & Myung, 2005). In the presence of a dysfunctional oculomotor system, visual performance is expected to degrade (Van Orden, Jung & Makeig, 2000). However, task performance may not reflect the physiological cost of mental workload (Backs & Seljos, 1994; Svensson, Angelborg-Thanderez, Sjöberg & Olsson, 1997).

The results of retrospective subjective tests, task performance, and physiological measurements of workload may not support one another. Sources of the discrepancy between workload metrics may be inefficiency in physiological measures, subjective tests, or performance results to reflect workload level. Based on the Multiple Resources Theory, indicating the selective sensitivity of physiological tests to task type and condition, using more than one test has been suggested for the evaluation of the amount of workload (Wickens, 2002; Ryu & Myung, 2005).
This thesis has considered subjective tests, task performance, and physiological measures to evaluate the level of workload. Among physiological measurements of mental workload, this thesis has used changes in cardiovascular measurements, skin conductance level, and changes in pupil size to indicate mental effort. The changes in the physiological measurements induced by mental workload could be distinguished from the changes induced by psychological states, such as arousal, if the results of subjective tests were in agreement with the physiological measurements. The expected effects of mental workload on these measures have been explained below.

1.2.1. **Heart rate**

Mental processing suppresses the baroreflex, which controls blood pressure via heart rate (HR). Higher HR and lower heart rate variability (HRV) are expected as a function of increased mental processing (Aasman, Mulder & Mulder, 1987; Mulder, 1988).

Decreased HRV has been shown during mental effort and dual binary choice tasks (Kalsbeek & Sykes, 1967; Lee & Park, 1990). Comparison of several cardiovascular measurements, task performance, blink and respiration at different levels of task difficulty showed heart beat intervals as the most sensitive indicator of mental effort (Veltman & Gaillard, 1996; Veltman & Gaillard, 1998). It can also give evidence of greater information analysis and a higher level of attention being devoted to protect task performance (Svensson et al., 1997). However, HR and HRV can respond to task demands specifically. It has been shown that HRV changes due to cognitive load or decision-making situations, while HR responds to the overall workload, or the perception of a higher load (Tattersall & Hockey, 1995). Comparing the results of a laboratory test and an aviation experiment suggested HRV can be a suitable measurement to differentiate fluctuations at low to intermediate levels of mental workload, while HR has been suggested to be more sensitive to distinguishing fluctuations at high levels of workload (De Rivecourt, Kuperus, Post & Mulder, 2008). However, Ryu and Myung (2005) found HRV was sensitive to difficulty levels of tracking, but did not respond to difficulty levels of memory tasks such as mental arithmetic. Some studies have found HRV to be sensitive to working memory tasks such as mental arithmetic (Mulder & Mulder, 1981; Carroll, Turner & Prasad, 1986; Aasman et al.,
1987). It has been reported that an increase in HR can indicate the level of subjects’ engagement with the arithmetic task (Carroll et al., 1986). HR has been found to be more sensitive to a difficult arithmetic task than one that was either easy or too difficult to perform (Carroll et al., 1986). Wilson (1992) suggested HRV is sensitive only to high cognitive demand and HR more sensitively indexes changes in the amount of information being processed. Similarly, Veldman (1992) found better results for HR and reported that at a sustained mental load (up to 45 min), only heart rate remained sensitive and could reflect a stressor.

Mental arithmetic is a complex function that is widely used in cognitive ability studies, and it particularly influences the process of working memory. Both systolic and diastolic blood pressures have been shown to significantly increase during arithmetic tasks, while sympathetic activity is slightly greater (Veltman & Gaillard, 1998). HR has been found to be unaffected by the non-psychological component of verbalization during a mental arithmetic task (Seraganian, Szabo & Brown, 1997). Bernardi et al. (2000) suggested increased HR measured as the number of inter-beat (R-R) intervals, and decreased HRV measured as the standard deviation of R-R intervals, can be used to investigate stress effects of a task since they avoid the influences of verbalization and breath patterns on test results.

This project has measured HR to investigate the effects of task conditions on both normal and nystagmus subjects. To accomplish this, we have compared HR across task conditions and at rest, to indicate different levels of task difficulty during visual tasks with and without high mental workload. We have measured HR as the number of beats per minute. Mental workload and task difficulty can be deduced as evidenced by HR changes.

1.2.2. **Skin conductance level (SCL)**

Frontal, prefrontal, parietal and anterior cingulate cortex, which contribute to attention and decision-making, have also been known to affect skin conductance level (SCL). In contrast with other physiological measurements of mental load such as heart rate and pupil size that are influenced by both sympathetic and parasympathetic systems, changes in SCL reflect the activation of only the sympathetic system (Critchley, 2002). Difficult situations that may require mental energy through the sympathetic branch can increase physiological arousal (Salvia, Guillot
SCL changes with variations in general excitation level and is influenced by task demands. SCL sensitively responds to the difficulty level when an overt (verbalization or eye movement) or covert (thinking and decision making) response is required (Tursky, Schwartz & Crider, 1970). A significant correlation has been found between increased SCL and mental stress induced by video games (Lin, Imamiya, Omata & Hu, 2006). Increased SCL has also been found with high levels of cognitive load in multimodal computer users (Shi, Ruiz, Taib, Choi & Chen, 2007). Higher levels of task involvement in mental arithmetic and longer information processing have been found to be associated with changes in SCL with longer duration (Vernet-Maury, Robin & Dittmar, 1995; Nourbakhsh, Wang, Chen & Calvo, 2012; Salvia et al., 2013).

Critchley, Elliott, Mathias and Dolan (2000) used a decision-making task (card playing) and found that changes in parietal and cerebellar activity co-varied with changes in SCL. The results indicated integration between cognitive and emotional aspects of behavior. However, larger changes in SCL have been measured under psychological stress when compared to mental stress (Setz et al., 2010). Sun et al. (2012) measured changes in SCL when subjects were required to perform both the Stroop test, a test in which participants were required to name the color of a word instead of what color the word says (Stroop, 1935), and mental arithmetic within a limited time. He investigated mental stress at different levels of physical activity including sitting, standing and walking. The results showed that mean SCL changes could sensitively differentiate mental stress conditions, regardless of the subjects’ physical activity (Sun et al., 2012).

This project has measured SCL to investigate the effects of overall workload induced across task conditions in both normal controls and participants with infantile nystagmus. The workload can be deduced from a significant change in SCL from baseline level (explained later in details).

1.2.3. Pupil size

Pupil dilation, due to both inhibited parasympathetic and evoked sympathetic effects, can reflect the amount of information being processed during post-stimulus time (O’Neill & Zimmermann, 2000). The relation between pupil response and activity of the frontal cortex, which contains both emotional and cognition related efferent nerves, has been demonstrated by functional magnetic resonance imaging (fMRI) (Siegle, Steinhauser, Stenger, Konecky & Carter, 2003). Also, under constant illumination conditions, iris dilator muscles can be activated by
norepinephrine, while noradrenergic mechanisms are known to be involved in cognitive functions associated with memory, attention, reward, behavior, and decision-making (Einhäuser, Koch & Carter, 2010).

Previous studies have shown that pupil dilation reliably indicates a moment to moment increase in processing resource utilization during a cognitive task, regardless of whether sensory, emotional, memory, or a complex of various functions are being examined (Granholm, Asarnow, Sarkin & Dykes, 1996). Pupil dilation has been observed in relation to active task processing, task related anxiety, and information overload (Peavler, 1974). Greater pupil dilation has been measured due to greater cognitive load, indicating a higher level of task difficulty and information processing of mental work (Hess & Polt, 1964; Kahneman & Beatty, 1966; Karatekin, 2004; Steinhauer, Siegle, Condray & Pless, 2004). Changes in pupil size can reflect the rate of mental effort allocated to a task. Pupil size increases systematically with more cognitive and information processing demands, until processing demands exceed available cognitive resources (Granholm et al., 1996; Van Orden, Limbert, Makeig & Jung, 2001; Karatekin, 2004; Jainta & Baccino, 2010). Pupil dilation is sustained as cognitive processing or attention is sustained, and this is, therefore, an effective measure (Siegle, Steinhauer, Carter, Ramel & Thase, 2003; Causse, Sénard, Démonet & Pastor, 2010).

Positive changes in pupil diameter have been found to be consistent as cognitive load increases. The concurrent time course of pupil dilation and increased activity in the middle frontal gyrus, one-third of the frontal lobes in the brain, as seen by fMRI during a memory task, provided more evidence relating pupil size to effective brain activity (Siegle, Steinhauer, Stenger, et al., 2003). Pupil dilation has been found to be associated with the cortical areas activated with sustained attention and continuous information processing during mental effort, i.e. frontal and parietal areas (Sarter, Givens & Bruno, 2001).

An increase in pupil diameter due to time-forced tasks shows the dominant activity is of the sympathetic system. Task-induced stress in the absence of emotional stress has been found to increase sympathetic activity and decrease parasympathetic inhibitory system activity, which can also result in increased pupil size (Ohsuga, Shimono & Genno, 2001; Steinhauer et al., 2004; Yamanaka & Kawakami, 2009). Pupil dilation has occurred during the performance of an arithmetic task, even when the sympathetic drive to the dilator muscle was blocked by
Dapiprazole (Steinhauer et al., 2004; Jainta, Hoormann & Jarchinski, 2008). This result suggests the major effect of the task demands on dilation of the pupil is evoked by cortical inhibition of the parasympathetic system, thereby blocking the sphincter muscle of the iris (Steinhauer et al., 2004; Jainta et al., 2008). Larger pupil size has been measured at higher difficulty levels of an arithmetic task, while less mental effort during an arithmetic task results in less pupillary dilation, although the dilation peaks in a shorter time (Boersma, Wilton, Barham & Muir, 1970; Ahern & Beatty, 1979).

In this thesis, pupil size has been used as an indicator of mental effort. To accomplish this, we have compared the changes in pupil size from baseline (explained later in detail) during the visual tasks with and without mental load. We can infer higher levels of mental effort and cognitive demands if we find larger pupil size.

Explaining the effect of cognitive load on nystagmus requires a review of the main characteristics of nystagmus. Below, nystagmus has been described. Then, the clinical findings and the effects of the cognitive load will be discussed with respect to visual demand, secondary task, and mental workload.

2. Nystagmus

2.1. Definition and prevalence

Nystagmus has been defined as involuntary ocular oscillations in which slow phase movements take the eyes away from desired gaze position or target of interest. These are followed by a return phase, which is more commonly a fast eye movement, or, in less common cases, a return slow eye movement, or a combination of both. The nature of the fast phase in nystagmus is corrective, while slow phase eye movements are responsible for rhythmic oscillations (Yee, Wong, Baloh & Honrubia, 1976; Van Vliet, 1982; Leigh, Dell'Osso, Yaniglos & Thurston, 1988). It has been found that the fast phase of nystagmus shares similar pathways with saccades towards a target (Worfolk & Abadi, 1991). Subsequent findings suggest that
nystagmus is more common in the general population than has been previously thought, and is estimated to affect 24.0 per 10,000 population (Sarvananthan et al., 2009).

2.2. Categories

Three categories of nystagmus are physiological nystagmus, acquired nystagmus, and infantile nystagmus. Physiological forms of nystagmus include end-point nystagmus, seen when holding far eccentric gaze; optokinetic nystagmus, seen when looking at a large moving field; and vestibular nystagmus, which is induced by self-motion or irrigating the ears unilaterally by warm or cold water (Abadi & Bjerre, 2002).

The acquired forms of nystagmus mainly result from vestibular and neurological diseases that can affect mechanisms in the brain that are responsible for controlling eye movements. It is important to distinguish between acquired and benign forms of neonatal nystagmus because of the difference in prognosis and management if acquired neurological disease is found to be present (Willshaw, 1993; Hertle, 2010).

Two main groups of benign infantile nystagmus have been described as infantile nystagmus syndrome (INS, which is more familiarly if less precisely known as congenital nystagmus) and fusion maldevelopment nystagmus syndrome (FMNS, previously known as latent or manifest latent nystagmus). A mixture of INS and FMNS can also be observed in some subjects (Dell'Osso & Daroff, 1975; Dell'Osso, Ellenberger, Abel & Flynn, 1983).

Lack of binocularity during visual system maturation is known to be the main factor associated with FMNS, while it has an almost obligatory relationship with the presence of strabismus (Dell'Osso, 1984; Abadi, 2002). Improving binocular vision through strabismus surgery has been suggested as the main method to reduce this kind of nystagmus (Zubcov, Reinecke, Gottlob, Manley & Calhoun, 1990; Gresty et al., 1992). However, extra-ocular muscle surgery can also be done in INS and can improve abnormal head posture, and result in broadening the field of high quality visual function (null area) especially if done under age two (Lee, 2002; Hertle et al., 2003; Hertle, Dell’Osso, FitzGibbon, Yang & Mellow, 2004; Wang, Dell’Osso, Jacobs, Burnstine & Tomsak, 2006; Wang & Dell'Osso, 2007b; Dell'Osso & Wang,
Contact lenses can be used as another way to dampen the effects of nystagmus, to broaden the null area and increase visual related quality of life in INS (Biousse et al., 2004; Taibbi, Wang & Dell’Osso, 2008).

Both INS and FMNS can be associated with sensory defects due to impaired vision, such as ocular albinism, optic nerve hypoplasia, achromatopsia, and congenital cataracts. They may also occur in the absence of any ocular or central nervous system abnormalities. This can be concluded only in the absence of any other underlying defects and after the exclusion of any underlying sensory deficient (Gelbart & Hoyt, 1988; Casteels, Harris, Shawkat & Taylor, 1992; Willshaw, 1993; Abadi, 2002). The form of INS without an associated sensory deficit is the most common group of pathological nystagmus (Abadi & Scallan, 2000; Abadi, 2002; Abadi & Bjerre, 2002; Hertle, 2008). It has been defined as binocular, grossly conjugate, and most often uniplanar horizontal nystagmus that usually presents at or shortly after birth (Dell'Osso & Daroff, 1975; Yee et al., 1976; Dell'Osso, 1984; Abadi & Dickinson, 1986; Hertle & Dell'Osso, 1999; Abadi, 2002; Abadi & Bjerre, 2002; Abel, 2006). Gresty et al. (1991) reported what appeared to be INS developing in teenagers or adults without any obvious trigger. Also, it is known that nystagmus may not be detected until later in life due to the presence of normal visual acuity, the presence of only small oscillations, and the absence of routine ocular examinations (Abel, 2006).

2.2.1. Infantile nystagmus syndrome (INS)

Nystagmus has been described by the characteristics of its waveform, including peak to peak amplitude, frequency, and time course of eye movements (Yee et al., 1976; Abadi & Dickinson, 1986). Nystagmus can be evaluated by measuring frequency, amplitude, intensity and foveation period duration. Nystagmus intensity is the product of frequency × amplitude. Foveation period duration (FP) is defined typically as those times within a cycle during which the foveation criteria are met (Dell'Osso & Daroff, 1975; Dell'Osso, Van der Steen, Steinman & Coleewijn, 1992; Erchul, Dell'Osso & Jacobs, 1998), e.g., eye velocity ≤ 4°/sec and eye position within ±2.00° of the desired target. These thresholds were used as foveation criteria by recent studies.
which investigated the effects of task conditions on nystagmus (Tkalcevic & Abel, 2005; Wiggins et al., 2007; Cham et al., 2008b; Cham, Anderson & Abel, 2013; Jones et al., 2013). Figure 1 shows the FP in a subject with INS while the foveation window has been defined using the criteria of eye position within ±1° of the desired target and eye velocity ≤4°/sec.

Figure 1: Foveation period in nystagmus waveform (Wang & Dell’Osso, 2009).

The performance of daily tasks can be complicated for nystagmus subjects (McLean, Windridge & Gottlob, 2012). This thesis pays special attention to INS waveforms and the two common symptoms of patients with INS, being “poor” vision and “slow to see”, while simultaneously investigating the effects of visual demand and mental load on these features. First, the INS waveform parameters will be defined. Then, the concepts of foveation period and null position in nystagmus will be explained. At a further section, we discuss the complaints of “seeing worse” and being “slow to see” in INS subjects.
2.2.1.1. **Waveform**

To clarify nystagmus characteristics, eye movement recording is essential, since ocular observations cannot identify all diagnostic details (Hertle & Dell'Osso, 1999). Figure 2 illustrates the common forms of nystagmus waveforms that can be recorded by oculographic techniques. A pendular nystagmus waveform resembles a sine wave oscillation, whilst jerk nystagmus consists of an accelerating slow phase that takes the eyes away from the fixation point in one direction, followed by a corrective fast phase that brings the eyes back. As described before, INS is binocular, grossly conjugate, most often uniplanar, and in the horizontal plane (Dell'Osso & Daroff, 1975; Yee et al., 1976; Abadi & Dickinson, 1986; Hertle & Dell'Osso, 1999; Abadi, 2002; Abadi & Bjerre, 2002).

![Figure 2: “Common patterns of nystagmus waveforms including pendular nystagmus (A), jerk nystagmus, i.e. typical infantile nystagmus syndrome with accelerating exponential slow phase velocity (B), fusion maldevelopment nystagmus syndrome with decelerating exponential slow phase velocity (C) or a linear/constant velocity slow phase (D)” (Abadi & Bjerre, 2002).](image-url)
A horizontal jerk nystagmus with increasing velocity of slow phases typically indicates the congenital form of infantile nystagmus (INS). Conversely, linear or decreasing velocity slow phases are indicative of acquired nystagmus, except in the case of FMNS, in which the velocity profile of slow phases is decreasing or linear (Dell'Osso, 1984). The waveform differences make INS and FMNS distinguishable from each other. In FMNS, the jerk phase always beats toward the fixating eye (Erchul et al., 1998; Abadi & Scallan, 2000; Abadi, 2002). This is also true of INS with a latent component (Dell'Osso, 1984). However, several less common waveforms such as multidirectional waveforms with vertical, oblique and circular directions, or triangular linear slow phases have been recorded in some subjects with congenital nystagmus (Dell'Osso & Daroff, 1975; Yee et al., 1976; Shawkat et al., 2000). Though there are individual differences in nystagmus waveforms within and between subjects, only twelve distinct nystagmus waveforms have been described in INS (Dell'Osso & Daroff, 1975).

The intensity (frequency × amplitude of nystagmus waveform) of INS may increase at away from a specific gaze position; i.e. null position. The nystagmus disappears with sleep and decreases with eye closure (assuming a low level of effort to see), and may damp in convergence or in a particular position of gaze (Wybar, 1969; Abadi & Dickinson, 1986; Ukwade & Bedell, 1992; Hertle et al., 2002; Wang & Dell’Osso, 2009). However, convergence may not always lead to nystagmus damping or to better visual acuity, with inverse effects even being reported in some INS cases (Von Noorden & La Roche, 1983; Ukwade & Bedell, 1992).

The nystagmus pattern varies in (a) periodic alternating nystagmus when beats horizontally in one direction, followed by a quiet period, and then reappears in the opposite direction. The period of jerk nystagmus in each direction can be similar with equal intervals between them, as is seen usually in acquired periodic alternating nystagmus (PAN). Some INS subjects may also exhibit alternating periods of jerk nystagmus, usually with unequal periods of jerk beats and asymmetric length of quiet intervals known as asymmetric aperiodic alternating nystagmus (APAN). Thus, the null zone -where minimum nystagmus intensity can be measured (Abadi & Bjerre, 2002)- can shift across gaze angles based on being regular or irregular (periodic or aperiodic form) and having equal or unequal intervals (symmetric or asymmetric form). Due to variations in nystagmus waveform and dynamic position of the neutral zone - where the nystagmus reverses- (Abadi & Dickinson, 1986; Leigh, 1992; Abadi & Pascal, 1994; Gradstein,
Reinecke, Wizov & Goldstein, 1997; Hertle, Reznick & Yang, 2009), this thesis has not included subjects with PAN or APAN pattern since there would be no way to control where in the APAN cycle task changes would be made. Figure 3 shows how changes in nystagmus waveform make a dynamic null zone in asymmetric, (a) periodic alternative nystagmus (Hertle & Dell'Osso, 2013a).

Figure 3: Illustration of shifting in the null zone due to changes in the nystagmus waveform, which accounts for the direction of asymmetric, (a) periodic alternative nystagmus. JL, jerk left; JR, jerk right (Hertle & Dell'Osso, 2013a).

2.2.1.2. Worse to see

Reduced visual acuity in nystagmus compared to normal-sighted individuals is a common finding among INS patients (Abadi & Bjerre, 2002). Degraded quality of vision has been reported in individuals with INS and can give the impression of seeing “worse” than normal, a complaint that has been improved in many INS subjects after the tenotomy procedure. That is, individuals see subjectively “better” post-tenotomy due to a possible improvement in visual acuity (Wang & Dell’Osso, 2008).

Some previous studies found visual acuity to be independent of INS intensity within subjects (Yee et al., 1976; Abadi & Worfolk, 1989). A significant correlation has been reported between
clinical visual acuity and foveation time (FP) between individuals with INS (Abadi & Worfolk, 1989; Guo, Reinecke & Goldstein, 1990; Dell'Osso & Jacobs, 2002). Changes in stability and duration of the FP has been shown, at least in some patients, to be related to the absence of oscillopsia, which is defined as the subjective impression of movement of the stable external world (Abel, Williams & Levi, 1991; Dell'Osso & Leigh, 1992; Hertle, FitzGibbon, Avallone, Cheeseman & Tsilou, 2001; Abel & Malesic, 2007). However, Bedell and Loshin (1991) found that none of the INS parameters were correlated with visual acuity within subjects. It has been argued that improvement in FP does not necessarily improve visual acuity since using brief flashes of big gratings to eliminate the retinal image motion did not cause a significant change in visual acuity for INS subjects with no apparent sensory abnormality (Dunn et al., 2014). Recently, it has been reported that internal states can change visual acuity irrespective of, or even in the opposite direction to, the changes in FP. It is suggested that visual acuity can be influenced by temporal summations of foveation times within subjects; that has been termed “total exposure time” in patients with INS (Jones et al., 2013).

In most patients, minimum nystagmus intensity can be measured at a particular region of gaze, termed the null zone, whose location varies between patients (Abadi & Bjerre, 2002; Hertle & Dell'Osso, 2013b). Although the null position is located at the central gaze position in most INS subjects (Figure 4), its location varies across INS subjects (Abadi & Bjerre, 2002). If the region of the null does not coincide with primary position, a change in head position is often adopted to resolve fine details (Gresty et al., 1984; Abadi & Dickinson, 1986; Abadi & Bjerre, 2002; Hertle & Dell'Osso, 2013b). Wang and Dell’Osso (2008) described seeing “better” and “more” as the outcomes of INS therapies, respectively due to improvement in FP duration and broadened null position, i.e. that refers to the wider high-quality foveation visual field in INS.
Figure 4: “Distribution of the null position across gaze angles in 143 INS subjects regardless of being idiopathic, albino, or with an ocular anomaly. Subjects with either fusion maldevelopment nystagmus or dynamic null position are not included.” (Abadi & Bjerre, 2002).

2.2.1.3. **Slow to see**

INS subjects have been reported to have an impression of taking a longer time to recognize visual objects, a phenomenon which has been termed “slow to see” (Sprunger, Fahad & Helveston, 1997; Wang & Dell'Osso, 2007a). This complaint can be improved in many INS patients after INS therapies such as the tenotomy procedure; that is, patients then recognize visual objects more quickly post therapy (Sprunger et al., 1997; Wang & Dell’Osso, 2008; ElKamshousy et al., 2012). The time taken to recognize a visual target (target recognition time) has been proposed as an indicator of visual function in nystagmus subjects. Visual recognition time can reflect changes in INS visual function even in the absence of marked change in visual acuity after INS therapy (Sprunger et al., 1997; ElKamshousy et al., 2012). Longer recognition time has been reported for both dynamic (moving to the right or left side with a random order velocity) and static visual targets across gaze angles in INS subjects when compared to normal subjects (Hertle et al., 2002). Longer recognition time in INS subjects than normal subjects did
not only occur when visual targets were presented at fixation position, but also when visual targets were presented at post-saccadic gaze positions (Hertle et al., 2002; Jones et al., 2013; Dunn et al., 2015).

It has been reported that the amplitude of prosaccades and final eye positions during a saccade task can be influenced by the direction of the presented target to slow phase of the INS cycle (Bedell, Abplanalp & McGuire, 1987; Worfolk & Abadi, 1991). INS subjects can acquire a new target position stepped to the same direction of INS slow phase more frequently using hypometric saccades or slow eye movements. Contrarily, Worfolk and Abadi (1991) measured the eye position during foveation time at the new target position and reported that INS subjects frequently showed normal responses for targets displayed on the opposite side and overshoot responses for targets displayed on the same side to the direction of INS slow phase. Worfolk and Abadi (1991) suggested that common neural pathways are being used to program the intrinsic saccades in an INS cycle and the visually guided saccades.

In a more recent study, Wang and Dell'Osso (2007a) used computer simulation to study INS during a saccade task. The results showed when a visual target stepped to a new gaze position, INS condition used different strategies to get on to the visual target that varied more for large (>10°) target steps. Figure 5 shows a sample of different strategies that are used in INS to refixate, including reflexive saccades, changes in nystagmus cycle, or a combination of both (Wang & Dell'Osso, 2007a). INS subjects are able to execute voluntary saccades with normal velocity-amplitude relationships (Yee et al., 1976; Wang & Dell'Osso, 2007a). However, both latency of saccades (Ls) and target acquisition time (Lt) have been found to be longer in INS subjects than normal subjects (Wang & Dell'Osso, 2007a; Dunn et al., 2015). The results obtained by Wang and Dell'Osso (2007a) indicated that increased Ls in the INS group compared with the normal group was not sufficient to explain subjective reports of seeing slow in INS. Instead of saccade latency causing the condition of “slow to see,” Wang and Dell'Osso (2007a) suggested that lengthened target acquisition time results in the phenomenon of being “slow to see” in INS. The cumulative effect of delayed saccade latency in INS has also been suggested to significantly impair visual performance compared to normal subjects, especially in busy visual environments such as during sport playing (Dunn et al., 2015). Dunn et al. (2015) measured recognition time, start time and end time of the saccade that positioned the eye on to the target.
presented at 3° vertically in both normal and INS groups. The results showed saccade duration, and the time taken to process the visual information after refixation, were similar between groups. However, recognition time was delayed in INS subjects when compared to normal subjects. This was mainly due to the prolonged saccade latency rather than slowed processing of visual information after target acquisition. Dunn et al. (2015) suggested two possibilities for longer saccade latency in INS compared to normal subjects. The first is difficulty in saccade execution that can lengthen the visual recognition time required for the object of interest. The second is a degraded level of visual awareness during non-foveating periods of the INS cycle, in the case of a less salient stimulus rather than a spot of light being presented. Although both of the above possibilities for delayed saccade latency in INS require further investigation, the latter one is also consistent with prolonged recognition time for static targets, such as acuity targets presented at a fixed gaze position (Hertle et al., 2002; Jones et al., 2013; Dunn et al., 2014). The results of Dunn et al. (2015) agreed with Wang and Dell'Osso (2007a), who suggested that target recognition delays were due to lengthened target acquisition time. While Wang and Dell’Osso (2007a) suggested that increased saccade latency in INS cannot explain the phenomenon of being slow to see in INS, Dunn et al. (2015) suggested that a cumulative effect of increased saccade latency contributes to delays in target acquisition and response to a post saccade target.

Unlike target recognition time that has been found to be affected by gaze position in INS (Hertle et al., 2002), longer saccade latency and target acquisition time in INS subjects, compared to normal subjects, are unaffected by the amplitude or direction of saccades (Wang & Dell'Osso, 2007a). Figure 6 shows saccade latency, target acquisition time, and stimulus time within an INS cycle (TC). Normalised TC (TC%) has been found as the main influencing factor on the latency of target acquisition (Lt), indicating that Lt could increase if the time of the target-step was during or close to the intrinsic saccades within a cycle (Wang & Dell'Osso, 2007a).

Prosaccades have been found to be unaffected by changes in foveation time due to tenotomy, and no marked change was found in saccadic latency with foveation improvement (Wang, Dell’Osso, Zhang, Leigh & Jacobs, 2006; Wang & Dell'Osso, 2007b; Wang & Dell’Osso, 2008). Longer target acquisition time in nystagmus subjects was also found with a pursuit task, which was thought to be due to the poor quality of foveation rather than to the saccadic components of the nystagmus waveform (Wang & Dell’Osso, 2009). An improvement in foveation period and
null zone width was found after horizontal rectus muscle tenotomy and reattachment, either alone or combined with recession, resulting in decreased target acquisition time in a saccadic task (Dell'Osso, 1998; Hertle et al., 2003; Hertle et al., 2004; Wang & Dell'Osso, 2007b; Wang, Dell’Osso, Tomsak & Jacobs, 2007; Wang & Dell’Osso, 2008). However, no relationship was found between the amount of improvement in target acquisition time, foveation, or visual acuity. Moreover, the amount of improvement in visual acuity and foveation quality was not related to the amount of the improvement in target acquisition time. Nevertheless, comparison of pre- and post-tenotomy results suggested shorter target acquisition time after foveation betterment as a possible explanation for an improvement in the condition of being “slow to see” (Wang & Dell’Osso, 2008).

It has been shown that both nystagmus parameters and visual function in INS subjects can be significantly affected by internal states such as time restriction, mental stress, or arousal (Yang et al., 2005; Cham et al., 2008b, 2013; Jones et al., 2013). Whereas INS parameters can be changed due to task conditions, including visual demand and internal states (Wiggins et al., 2007; Cham et al., 2008b; Jones et al., 2013), there is a possibility that target acquisition and visual processing time can be affected by task conditions. Here, we defined visual processing time as the time taken to respond to a visual target after it has been foveated. This time duration is similar with the time duration used by Dunn et al. (2015) to compare visual processing time between normal controls and patients with INS; while it includes both collecting and processing the visual samples.

This project aims to investigate how task conditions, which are changed by manipulating cognitive load, can have an effect on two common complaints of INS subjects being “worse to see” and “slow to see”. We have provided general information about being “worse to see” and “slow to see” in patients with INS. Now, we wish to explain the previous findings on the effects of task conditions and internal states on patients with INS and normal-sighted people.
Figure 5: Samples of foveating strategies in subjects with infantile nystagmus syndrome in response to small–size target steps (left) and large–size target steps (right) (Wang & Dell'Ossio, 2007a).
Figure 6: Illustration of stimulus time within a nystagmus cycle (Tc), latency of an initial saccade (Ls) and the target acquisition time (Lt) in one nystagmus subject (Wang & Dell'Osso, 2007a).

3. Cognitive load in visual tasks

As explained before, this project has paid special attention to the effect of internal states on INS subjects. To better explain how cognitive load can have an effect on nystagmus, we should first review below the extent that eye movements can be affected by workload in normal subjects. Following this review, the effects of visual demand and mental load in nystagmus will be discussed.
3.1. **In normal controls**

3.1.1. **Fixation task**

Increased demands in visual scanning tasks have led to a decrease in fixation duration and an increase in fixation rate. With the introduction of a secondary task, fixation duration increases and fixation rate decreases (Callan, 1998; Tsai, Viirre, Strychacz, Chase & Jung, 2007). The effect of task condition on refixations, such as those made during a visual search task, has been found to be highly dependent on task context (Duchowski, 2002; Magedman, 2010; Schulz et al., 2011).

Task conditions have also been found to have an effect on microsaccades, which are binocular saccades with an amplitude less than 1 degree, and can be recorded during a fixation task (Engbert & Mergenthaler, 2006). However, a few studies are available that investigate the nature and characteristics of microsaccades, e.g., as follows. Investigation of microsaccades during maintaining fixation, free viewing, and visual acuity demanding task conditions has suggested that microsaccades contribute to fine visual acuity and exploring visual details when increased during acuity demanding tasks (Ko, Poletti & Rucci, 2010). A later study showed that attentional shifts had an effect on directions of microsaccades and rate of microsaccades positively correlated with the level of visual demand (Hicheur, Zozor, Campagne & Chauvin, 2013).

Since this project does not have the intention to measure microsaccades or fixation in normal subjects, the effects of task condition have been reviewed specifically only in regard to saccade tasks in normal subjects.

3.1.2. **Saccade task**

Before reviewing the literature about the effects of a high mental workload on saccades, we briefly review the main areas of the brain that are involved in the execution of saccades. Following this, we will discuss the previous literature about changes in the characteristics of saccades during manipulation of mental load and of secondary task conditions.
3.1.2.1. Saccades execution centres

The cortical areas involved in generating saccades are the frontal eye fields, supplementary eye fields, the lateral intraparietal areas, and dorsolateral pre-frontal cortex. Subcortical areas, including superior colliculus, seem to be responsible for express saccades that are more primitive, but faster with a peak latency of 100 msec or less (Ikeda & Hikosaka, 2003; Johnston & Everling, 2008; Everling & Johnston, 2013). Express saccades are generated through the superior colliculus, while the cortex is responsible for initiating saccades with longer latencies. The superior colliculus receives projections from both the retina and frontal eye field (Mays & Sparks, 1980; Bruce & Goldberg, 1985). Attention and oculomotor processing are integrated tightly in the neural level of the parietal, frontal, and temporal lobes (Kustov & Robinson, 1996; Corbetta et al., 1998; Simon, Mangin, Cohen, Le Bihan & Dehaene, 2002). It is known that higher cortical areas, including frontal and supplementary eye fields, contribute to the controlled execution of saccades with a longer latency. The paramedian pontine reticular formation (PPRF), or horizontal gaze center which generates horizontal components of the saccades, is controlled by projections from the superior colliculus and direct projections from contralateral frontal eye fields (Moschovakis, Scudder & Highstein, 1996; Büttner-Ennever & Horn, 1997; Johnston & Everling, 2008). Moreover, the superior colliculus, which is responsible for automatic reflexive saccades, is also controlled by higher cortical areas, including the frontal and prefrontal dorsolateral cortex, unless it is impaired by cortical lesions, such as frontal lesions (Johnston & Everling, 2008; McDowell, Dyckman, Austin & Clementz, 2008; Müri & Nyffeler, 2008). Figure 7 shows the anatomy of the saccade controlling system (Johnston & Everling, 2008).
Figure 7: “Cortical and subcortical areas of the saccadic eye movement system of the monkey. Top: medial view; Bottom: lateral view. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; LIP, lateral intraparietal area; PPRF, paramedian pontine reticular formation; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; SC, superior colliculus; SEF, supplementary eye fields.” (Johnston & Everling, 2008).

3.1.2.2. Saccade velocity

Several studies have investigated the effects of task demands and internal states, especially on visually guided saccades/prosaccades (App & Debus, 1998; Montagnini & Chelazzi, 2005), which are the saccades that are aimed towards an eccentrically positioned target. App & Debus (1998) measured saccades under different post-saccadic visually demanding conditions, where subjects were required to respond to post-saccadic targets (e.g., responding to numbers from 2-5, and the direction they presented on the screen i.e. left or right). The results showed that the effort applied under higher post-saccadic demands increased peak saccadic velocity (PSV) in target saccades (saccades towards an eccentric target position when a choice response was required) compared to return saccades (saccades towards a central fixation target when no response was required), when only a basic activation level would be expected. However, the increase in peak saccadic velocity was dependent on post-saccadic demands, whereby increased post-saccadic demands led to increased peak saccadic velocity in return saccades, thereby demonstrating the influence of increasing visual motor demand on the PSV (App & Debus, 1998).
Consistent with this, Montagnini and Chelazzi (2005) used a discrimination task (e.g., identify E from F) under different task difficulties, and showed that post-saccadic task under difficult perceptual conditions revealed both an increase in peak velocity and a reduction in latency of saccades. The results suggested that perceptual urgency to perform a saccade can have an influence on both latency and peak velocity of saccades. However, no physiological or subjective measurement of task difficulty or mental workload was done, and only reduced task performance (response accuracy <75%) was used to determine the perception of urgency (Montagnini & Chelazzi, 2005).

Using complex visual tasks such as simulated flights or driving yielded inconsistent results for the velocity of saccades in the presence of variations in task difficulty and mental workload. Some studies found higher saccade velocity was associated with a higher level of cognitive workload, arousal, or level of vigilance (Di Stasi et al., 2009; Di Stasi, Marchitto, Antoli, Baccino & Cañas, 2010; Hirvonen et al., 2010; Di Stasi, Antoli & Cañas, 2011; Di Stasi, Contreras, Cándido, Cañas & Catena, 2011; Di Stasi et al., 2012; Di Stasi, Catena, Cañas, Macknik & Martinez-Conde, 2013). Cognitive control of saccade generation through reward expectation has been found to speed up both reflexive saccades in animals (Chen, Hung, Quinet & Kosek, 2013) and voluntary saccades in humans (Chen, Chen, Zhou & Mustain, 2014). However, a decrease in the velocity of saccades has also been measured when the mental workload and difficulty level of a visually demanding task increased (May, Kennedy, Williams, Dunlap & Brannan, 1990; Van Orden et al., 2001; Di Stasi, Renner, et al., 2010).

It is still not clear to what extent task conditions can affect the velocity of prosaccades in the presence of post-saccadic demand and mental workload. This thesis investigates changes in saccade velocity due to both post-saccadic demand and a high mental workload, and investigates any possible effect of saccade velocity on target acquisition time (the time taken to position the eyes on the desired target). The results can be useful in terms of cognitive demands and perceptual difficulty of task conditions, such as driving, when determining mental workload is important for work safety.
3.1.2.3. **Saccade latency**

Hallett and Adams (1980) proposed a model in which prosaccades are programmed automatically. However, a reflexive saccade needs at least 100 msec more than the time that is required to be generated (40 msec to transferring signal from retina to superior colliculus and 20 msec to trigger saccade). This delay exists because the superior colliculus is not working in isolation, but receives connections from a wide area of the cortex. Even the generation of a simple prosaccade is a result of the weighting of “bottom-up” signals that concern basic target properties such as luminance, size, and “top-down” signals that concern the observer’s current goals and intentions. On the other hand, the brain needs to work out whether the saccade is worth being elicited in relation to the cost of the current fixation target, and also to the limited processing resources (Carpenter, 1981, 2001; Hutton, 2008).

The study of reaction time can illustrate how decisions are made. Saccades provide us with a powerful tool to investigate cognitive control of behavior, especially those aspects involved in working memory, decision making, and attention (Hutton, 2008). Higher cortical areas that are involved in saccadic control play a key role in maintaining visual working memory and in avoiding unnecessary prepotent behavioral responses (Halliday & Carpenter, 2010). A well-known function of higher cortical areas is when subjects are doing the antisaccade task (looking at the opposite direction of a presented visual target) or no go tasks (not looking at the presented peripherally located visual target), both of which require the suppression of reflexive saccades through a supervisory cortical system. Performance of these tasks in the presence of frontal lesions reveals a higher error rate and an increased number of antisaccade errors, reflexive saccades with short latency (Guitton, Buchtel & Douglas, 1985; Schiller, Sandell & Maunsell, 1987; Pierrot-Deseilligny, Rivaud, Gaymard & Agid, 1991; Braun, Weber, Mergner & Schulte-Mönting, 1992). Similarly, a high level of mental workload weakens cortical control of the superior colliculus, resulting in an increased error rate and proportion of short latency saccades at no go and antisaccade tasks (Roberts, Hager & Heron, 1994; Stuyven, Van der Goten, Vandierendonck, Claeys & Crevits, 2000; Mitchell, Macrae & Gilchrist, 2002; Halliday & Carpenter, 2010).

A simple model to understand how cognitive process can have an effect on the speed of saccade generation is the LATER model (Linear Approach to Threshold with Ergodic Rate) that has been developed by (Carpenter, 1981; Carpenter & Williams, 1995). The LATER model was
introduced based on the linear distribution on a reciprob plot of the reaction time in which the cumulative probability of latency on a probit scale is plotted versus reciprocal latency (Carpenter, 1981). In this model, a decision signal rises linearly from a baseline level of $S_0$ at a constant rate of $r$ until it reaches the threshold of $S_T$, at which point the saccade is triggered. Knowing that, the time between the start of the rise in the decision signal and crossing the response threshold will be $T=(S_T - S_0)/r$. Using reciprob plot in the LATER model, the slope of the line (rate of $r$) represents the supply of information that varies randomly trial by trial with the mean of $\mu$ and variance of $\sigma^2$. The initial value of $S_0$ refers to log prior probability of decision making and can determine the probability and expectation of a saccade. $S_T$ is a measure of priority and can refer to what extent the saccade is urgent (Carpenter, 1981; Carpenter & Williams, 1995). Figure 8 shows the LATER model and distribution of latency on a reciprob plot (Reddi, Asrress & Carpenter, 2003; Pearson, Raškevičius, Bays, Pertzov & Husain, 2014).

There is a fixed and competitive relationship between the parameters of the LATER model including $S_0$, $S_T$, $\mu$ and $\sigma^2$. The large value for $\mu$ comes with a small value for $\sigma^2$ and generates the main part of the distribution that identifies the higher cortical levels of saccade generation. The large value for $\sigma$ comes with a small value for $\mu$ close to zero and generates the initial part of distribution that identifies reflexive saccades with short latency generated at the superior colliculus (see Noorani (2014) for review). Changes in expectancy or sensory-related urgency of saccade execution tend to increase the number of early responses in the LATER model. An increase in the saccades with short latency will result in the latency distribution line swiveling about a fixed point corresponding to infinite time in the axis of reciprocal latency. This can be identified from the change in rate of raise to threshold ($r$) that causes a shift in the distribution line with no change in the slope of it (Similar $\sigma$ but varied $\mu$) in the LATER model (Reddi & Carpenter, 2000; Reddi et al., 2003; Sinha, Brown & Carpenter, 2006; Anderson & Carpenter, 2010; Pearson et al., 2014). Figure 9 shows changes in response threshold and rate of rise in decision signal, swivel and shift the line in LATER model respectively (Reddi et al., 2003; Sinha et al., 2006).
Figure 8: “Description of LATER model. Left: On presentation of a stimulus, a decision signal $S$ rises linearly from an initial level $S_0$ until it reaches the threshold $S_T$ when a response is initiated. The rate of rise in saccade decision signal varies randomly across trials about a mean $\mu$ and standard deviation $\sigma$ in a Gaussian manner, such that the distribution of latency is skewed (shaded area). This is reflected as an asymmetric cumulative density function. However, the reciprocit plot yields a straight line that allows parameters of the LATER model such as $\mu$ and $\sigma$ to be estimated” (Reddi et al., 2003; Pearson et al., 2014).

Cognitive processes can affect all three parameters of the LATER model to determine the speed of saccade generation (Hutton, 2008). Harwood, Madelain, Krauzlis and Wallman (2008) measured the latency of saccades when visual attention was required to look at a fixation point presented inside or outside of attended rings. The results suggested the level of attention allocated to the saccade target determined the latency of saccade through changes in saccade decision signal. The rate and rate variability of a decision signal can be changed in accordance
with the cost/benefit ratio of making the saccade in terms of visual benefits. The cost/benefit ratio

![Figure 9: Distinct effects due to changes in parameters of the LATER model. (a): Changes in baseline threshold ($S_0$) and execution threshold ($S_T$) causes the distribution line to swivel about the fixed point on the infinity axis. (b): Changes in the mean rate of rise in saccade execution signal ($\mu$) shifts the distribution line horizontally with fixed slope (Reddi et al., 2003; Sinha et al., 2006).]

can determine how urgent a saccade is. The oculomotor system can defer saccade execution or make long latency saccades when the saccade execution yields little visual benefit (Harwood et al., 2008). In other words, neural computations between prior probability, sensory inputs, and expected cost/benefit are combined into one likelihood ratio (LR) to generate a saccade, and that is the optimal decision signal based on the competing hypotheses for saccade execution (Gold & Shadlen, 2001; Harwood et al., 2008). Saccade latency can be decreased due to an increase in mean rate of rise in the decision signal as implicated in the perceptual urgency of saccade execution (Montagnini & Chelazzi, 2005) or by a lowering of the execution threshold, as is seen in the case of urgency of attention demanding post-saccadic targets (Reddi & Carpenter, 2000; Reddi et al., 2003). It has been shown that the threshold of saccade onset decreased in the case of high urgency of saccade performance, when subjects were instructed to perform saccades as
quickly as they could, even at the expense of their accuracy (Reddi & Carpenter, 2000; Reddi et al., 2003). Similar to the urgency of saccades, the requirement to perform a difficult perceptual judgment at the post-saccade position reduced saccade latency and also increased the velocity of saccades (Montagnini & Chelazzi, 2005). However, App and Debus (1998) found that a high post-saccadic demand level increased the velocity of saccades but failed to change saccade latency. One possibility is that different levels of sensitivity of the mechanisms which underlie saccade latency and velocity are affected differently by the demands of the task.

The neural basis of the LATER model can be explained by the integration among the saccade-signals that link cortex, basal ganglia, or thalamus (Romo & Schultz, 1987; Schultz & Romo, 1992). Inputs from the basal ganglia can determine the baseline level of saccade execution ($S_0$ in LATER model) and can inhibit unwanted saccades (Carpenter, 1999). At least a part of the large variability in saccade latency can be susceptible to modulation (especially reduction) through top-down task-dependent control mechanisms for saccade facilitation (Montagnini & Chelazzi, 2005). Inputs from the frontal eye field can reduce the latency of saccades through small variability and deep rate of rise in saccade latency (Carpenter, 1999), like the ones engaged in the perceptual urgency paradigm (Montagnini & Chelazzi, 2005). Neural recordings in monkeys have shown that reward manipulation in a saccade task increased two types of reward-related activity in the deep layers of the superior colliculus. One modulation was an increased anticipatory (lowered baseline) activity that enhanced saccade movement before saccade initiation (Ikeda & Hikosaka, 2003), that is, lower $S_0$ in the LATER model (Montagnini & Chelazzi, 2005). The other modulation was related to enhanced gain of activation after the onset of saccades and could be related to cortical signals, especially those from frontoparietal regions (Ikeda & Hikosaka, 2003); that is, the rate of rise in the saccadic decision signal in the LATER model (Montagnini & Chelazzi, 2005).

Measuring express saccades and saccade latency concurrently with performance of a discrimination task (identify E from 3) in a normal group showed that initiation of voluntary saccades was facilitated and the latency of reflexive saccades reduced under the overlap condition (when the central fixation point does not disappear at the time of saccade target presentation). However, the discrimination task did not affect production of express saccades (Van Stockum, MacAskill, Myall & Anderson, 2011, 2013). Accuracy of the discrimination task showed a significant direct relation with saccade latency. Saccade latencies significantly
increased (mean of 29 ms) when visual distracters were added to the discrimination task (Van Stockum et al., 2011).

Kristjánsson, Chen and Nakayama (2001) measured the latency of saccades when subjects were instructed to perform blocks of prosaccades (saccades aimed towards an eccentrically positioned target) and antisaccades, along with a discrimination task. The task was to determine the brighter target, or the one with a higher special frequency, by pressing a key. The results showed that reduced attention to the saccade task resulted not only in faster antisaccades, but in longer latency of prosaccades. The increase in latency of prosaccades was not significant when no response was required for the discrimination targets concurrent with prosaccades (Kristjánsson et al., 2001). The results were consistent with Stuyven et al. (2000) who suggested prosaccades are also vulnerable, albeit to a lesser degree, than antisaccades and that executive interference tasks can negatively affect prosaccade generation. Stuyven et al. (2000) investigated saccades in two antisaccade and prosaccade tasks with different levels of a secondary cognitive task. The secondary task was fixed or patterned key tapping. The results showed an increase in the latency of prosaccades with the presence of the cognitive task (patterned key tapping). The significant increase in latency of prosaccades in the presence of a concurrent task also has been shown by Mitchell et al. (2002) when subjects were required to do blocks of prosaccades and antisaccades at the same time of n-back task, a continuous performance task to measure working memory where the performer is required to remember the order of the presented stimulus (Kirchner, 1958).

In a previous study, Roberts et al. (1994) found no change in latency of prosaccades in conjunction with an arithmetic task, and measured no change in saccadic latency with this concurrent task. However, the arithmetic task consisted of simple addition problems (to add current sum or given number to a fixed or given number randomly from one to nine). No reliable correlation has been found between saccades and working memory capacity measured by the Span task, which reflects working memory capacity from the ability of recalling items from a presented list of items (Dempster, 1981). Using a go/no-go task showed that mental arithmetic degraded task performance. However, no physiological or subjective measurement of workload was taken to investigate the level of subjects’ effort or the mental load imposed by the arithmetic task concurrent with saccade tasks (Roberts et al., 1994). Although mean latency of prosaccades could indirectly predict the proportion of errors in an antisaccade task, that relationship was not
mediated by individual differences in working memory capacity (Crawford, Parker, Solis-Trapala & Mayes, 2011).

Recording eye movements in a no-go task under a mental load condition that was reflected in higher errors in secondary task performance, saying the opposite of the heard words, showed less inhibition of express saccades (Halliday & Carpenter, 2010). Interestingly, when the primary task was the antonym task, more reflexive saccades were recorded at both go/no-go trials (Halliday & Carpenter, 2010). This suggested that secondary tasks have shown inconsistent effects on latency of prosaccades due to the level of mental load, the context of the cognitive task, and the priority being distracter or saccade task (Roberts et al., 1994; Stuyven et al., 2000; Halliday & Carpenter, 2010).

The effects of mental workload and secondary tasks on eye movements are highly dependent on task context (Duchowski, 2002; Halliday & Carpenter, 2010; Magedman, 2010; Schulz et al., 2011). Investigation of the effects of post-saccadic demand (App & Debus, 1998) and a concurrent mental task (Roberts et al., 1994) on the characteristics of visually guided saccades revealed inconsistent results (Roberts et al., 1994; App & Debus, 1998). Using mixed antisaccade and prosaccade task have shown that a dual task condition increased the latency of prosaccades (Claeys et al., 1998; Stuyven et al., 2000; Kristjánsson et al., 2001; Mitchell et al., 2002). However, it is possible that the saccade inhibitory system interferes with the characteristics of prosaccades in a mixed antisaccade and prosaccade task (Roberts et al., 1994). This thesis aims to provide more information about the effects of cognitive tasks (a discrimination task with and without counting back) on prosaccades without any possible interference arising from antisaccades or go/no-go tasks. Moreover, using prosaccades concurrently with an optokinetic nystagmus task has shown that the effects of behavioral task vary between reflexive and intentional fast eye movements due to different mechanisms involved (Kaminiarz, Königs & Bremmer, 2009). We aim to compare the effects of a cognitive task on prosaccades between normal subjects and INS subjects. The results will aid the understanding of the mechanisms involved in saccade task in INS. The results can be also important in terms of task performance and work safety, when seeing at different gaze positions may be required in the presence of a cognitive load.
3.1.2.4. Secondary saccades and target acquisition time

Initial saccades do not usually bring the target exactly onto the fovea, but rather make it about 90% of the way to the target. Saccade undershoots that fall short of the target positions are followed by secondary saccades, which are corrective saccades generated to reduce final position error (Bartz, 1967; Becker, 1972). Secondary saccades can be recorded after the end of the initial saccade with a short latency of about 125 msec, about 50% smaller than the latency of the initial saccade (Bartz, 1967; Becker & Fuchs, 1969). It has been argued that secondary saccades are programmed internally to correct small residual retinal errors when the initial saccade is completed (Weber & Daroff, 1972; Prablanc & Jeannerod, 1975). Secondary saccades are not dependent on response feedback (retinal or proprioceptive) and can be made even when the final fixation point disappears (Becker & Fuchs, 1969; Weber & Daroff, 1972; Hallett, 1978; Henson, 1979). Larger amplitudes of initial saccade errors and production of more secondary saccades have been observed in the presence of discrimination tasks or randomly positioned targets (Henson, 1979; Kapoula & Robinson, 1986). Investigating initial and secondary saccades during scanning of stationary targets also showed a higher frequency of secondary saccades with more accurate final eye position (Wu, Kwon & Kowler, 2010). Similar to the initial saccades, secondary saccades contribute to target acquisition time and final end point position (Toyomura & Omori, 2003).

The final saccade end position and target acquisition time can affect performance in tasks in which subjects’ reaction to a visual target is required, such as driving. We could not find any article that investigated the effects of mental load on secondary tasks and target acquisition time. A previous study found that interruption of attention in the presence of a secondary task (reading and counting presented numbers above a visual target) or in a more complex condition (using an auditory cue alone rather than presenting a visual cue) increased target acquisition time (Pierno, Caria, Glover & Castiello, 2005). However, target acquisition time was defined as the time taken to get aligned with the visual target while both head and body movements were allowed. The data were recorded using a head tracker, while no data for eye movements were available. Data were also unavailable for eye movement reaction times (Pierno et al., 2005).

It may be that the proportion of secondary saccades can have an effect on the accuracy and time of target acquisition under different task conditions. However, it is still unclear to what
extent target acquisition time can be affected by differences in initial and secondary saccades due to secondary tasks and mental workload.

As explained later, individuals with infantile nystagmus suffer from being \textit{slow to see}, possibly because they have longer target acquisition times. The extent to which mental workload affects the phenomenon of being “slow to see” in nystagmus has not yet been investigated. This thesis aims to investigate to what extent cognitive load affects saccade execution, target acquisition time, and visual processing time within normal subjects and individuals with INS, and also to what extent these effects vary between INS and control groups. The results can be used to compare the visual function between normal and INS groups under high workload conditions such as driving, and when outcomes of nystagmus therapies are under evaluation.

3.2. In individuals with nystagmus

3.2.1. Fixation task

It has frequently been claimed that nystagmus worsens under psychological factors such as tiredness, anxiety, and the attention state of the subject (Dell'Osso, Flynn & Daroff, 1974; Dell'Osso, 1982; Abadi & Dickinson, 1986; Abadi & Scallan, 2000; Abadi & Bjerre, 2002). It has similarly been stated that “effort to see” and “fixation attempt” can reduce visual performance in nystagmus subjects (Dell'Osso & Daroff, 1975; Dell'Osso, 1982; Abadi & Dickinson, 1986; Abadi & Pascal, 1991; Abadi & Scallan, 2000; Abadi & Bjerre, 2002; Scheiman & Wick, 2002). The negative effects of psychological factors and task conditions on nystagmus has been widely accepted; however, only a few studies are available on them (Abadi & Dickinson, 1986; Tkalcevic & Abel, 2003, 2005; Wiggins et al., 2007; Cham et al., 2008b, 2008a; Jones et al., 2013). Even in this small field, results have proved inconsistent.

Abadi and Dickinson (1986) showed a nystagmus waveform change under fixation attempt. However, only one INS subject was investigated and the visual target, a LED, was not acuity demanding. Forced viewing time restriction has also resulted in a greater decrease in visual acuity in nystagmus subjects compared to normal subjects (Yang et al., 2005). However, the amount of mental effort expended by subjects was not clear. Also, there was no quantification as to how nystagmus parameters changed during the task. No quantitative study was conducted on
the effects of task-induced stress on nystagmus parameters until Tkalcevic and Abel (2005) recorded eye movements in nystagmus subjects during an acuity demanding task using Landolt C targets. The results did not show the expected result that increasing visual acuity demand alone would cause nystagmus parameters to deteriorate. However, no measurement was used to indicate the level of task-induced stress or effort to see in subjects during the tasks.

A further study by Wiggins et al. (2007) showed nystagmus intensity decreased and foveation time increased as the difficulty of an acuity task increased; that is, nystagmus improved with increased visual demand. However, the results of both Wiggins et al. (2007) and Tkalcevic and Abel (2005) might be due to the lack of the importance of performing the task for subjects. Moreover, no measurement of mental state was used.

Jones et al. (2013) found nystagmus deteriorated (intensity increased with shorter foveation periods) and subjects’ response time increased due to induced arousal. However, the arousal was elicited by the threat of an electrical shock, which is not similar to daily life stressors for most people. Cham et al. (2008b) used a visual task-induced stress paradigm whilst subjects were requested to do a mental arithmetic task during a time forced visual acuity test. The results showed nystagmus deteriorated during mental load, which was indexed by heart rate. Foveation time decreased significantly compared to when subjects were doing the task without mental arithmetic while significant differences were found for nystagmus parameters between low and high difficulty levels of a visual acuity task. However, the experimental paradigm was limited to primary gaze position while nystagmus parameters and visual performance in INS may be highly affected by gaze position (Abadi & Bjerre, 2002; Yang et al., 2005).

Since looking at different gaze locations is necessary under real world conditions, visual function in nystagmus subjects should be assessed across different gaze positions. Although it is known that the foveation period is highly dependent on gaze position in many individuals, no data are yet available on the effect of “effort to see” on foveation period for different gaze positions. This project aims to address to what extent nystagmus can change centrally in respect to acuity level and distance of the desired target from the null position. The results will provide more information about INS patients’ response to visual task demands and mental load at different target locations, and should be useful for situations in which subjects’ performance is critically important for work safety.
3.2.2. **Saccade task**

Prolonged latency of saccades (Ls) and target acquisition time (Lt) have been measured in infantile nystagmus compared to normal subjects (Wang, Dell’Osso, Zhang, et al., 2006; Wang & Dell'Osso, 2007a). The effects of internal states such as high mental workload during visually demanding tasks have been found on both fixation and prosaccade tasks in normal subjects (May et al., 1990; App & Debus, 1998; Van Orden et al., 2001; Tsai et al., 2007; Di Stasi, Renner, et al., 2010; Schulz et al., 2011). However, to what extent prosaccades can be influenced by central factors such as tiredness, vigilance, or high mental load in nystagmus subjects is still unknown. Effects of internal state have been shown on foveation and nystagmus waveform (Abadi & Dickinson, 1986; Cham et al., 2008b; Jones et al., 2013). Due to the potential for high visual acuity existing only for a small area of the retina, the fovea, eye movements are necessary to move the eyes between targets of interest in order to have a clear view of our visual environment. In individuals with INS, shorter Lt has been suggested due to longer foveation time (Wang & Dell’Osso, 2008; Wang & Dell’Osso, 2009), which itself can be affected by task conditions and internal state (Abadi & Dickinson, 1986; Cham et al., 2008b; Jones et al., 2013). Possible changes in foveation period due to more demanding task conditions in INS may result in target acquisition time worsening in INS. Hence, changes in mental state that increase target acquisition time could result in an exacerbation of being “slow to see” under task-induced stress in INS subjects. Moreover, although a similar time for processing of visual information has been measured between normal subjects and INS subjects (Dunn et al., 2015), no data is yet available from high cognitive load conditions. Differences in data between groups of participants (normal controls versus INS subjects), or the interaction between groups and task conditions (with or without cognitive load), will provide us with not only more information about what INS subjects perceptually experience in visual tasks, but also whether or not the condition of being “slow to see” in INS is caused by factors beyond delayed target acquisition. Whether or not visual processing time remains similar between INS and normal groups with mental workload has not been investigated yet. It has been suggested that patients with INS can resolve target details after it has been foveated through the temporal summation of sequential foveation periods that provide the “total exposure time” required to see an object (Jones et al., 2013). As both foveation period and INS frequency have been found to be affected by task conditions (Wiggins et al., 2007;
Cham et al., 2008b; Jones et al., 2013), visual processing time may be affected by task conditions.

Besides measuring FP which provides best potential visual acuity in INS (Dell'Osso & Jacobs, 2002), measurement ofLt has been suggested as a way to evaluate visual function in daily activities before and after nystagmus therapy (Wang & Dell’Osso, 2009). The effects of the mental state onLt might influence the clinical evaluation of the visual function in INS. However, as explained before, no data are yet available for this. A relationship found between changes inLt and foveation due to tenotomy (Wang & Dell’Osso, 2008) makes it worthwhile to know to what extent foveation, Lt, and saccadic parameters (including latency and gain) are influenced by internal responses to changes in mental load. Since it has been suggested that pathways involved in the programming of saccades towards a target also contribute to the programming of quick phases in INS (Worfolk & Abadi, 1991), our findings will help future nystagmus modeling and allow for better understanding of how nystagmus can change centrally.

We investigated to what extent INS changes due to cognitive load and stress level, while also assessing nystagmus under conditions more closely resembling daily tasks, when both frequent refixation and concurrent visual tasks may be required. To ensure that our method is suitable to induce mental stress within subjects, we first ran the experiments on a group of subjects with normal general health. If the results in the normal subjects could indicate induced mental stress, we then could run the same tasks in the group of subjects with nystagmus. By conducting the experiments in normal subjects, we not only tested our experiment protocols to induce stress, but also investigated to what extent mental load affected the contributing elements of post-saccade visual tasks in normal subjects. Those can include saccade generation, target acquisition time, the accuracy of final saccade end position, visual processing time, and task performance in terms of subjects’ reaction time and accuracy of submitted responses to a visual object. The next chapter explains in detail the experiments in normal subjects.
Chapter Three: Experiments in normal participants

1. Background and aim

Real world activities can combine visual elements concurrently with irrelevant mental tasks. An example of normal subjects being “slow to see” happens during driving when they look at but fail to see an object, or see it very late (Simons & Chabris, 1999; Simons, 2000; Beanland & Pammer, 2010). Recarte and Nunes (2003) reported an increase in target acquisition time in drivers when doing a task with a high mental load. A study by Pierno et al. (2005) showed that interruption of visual attention in the presence of a secondary task (reading and counting presented numbers above a visual target, or using an auditory cue alone rather than presenting a visual cue) increased target acquisition time. However, no data for saccades were provided. It is not clear whether the late target acquisition time found in the presence of a high mental load and secondary task (Recarte & Nunes, 2003; Pierno et al., 2005) can be generalised for saccade tasks. Moreover, the source of late target acquisition time with high mental load has not yet been made clear. There is a possibility that target acquisition time may increase as a function of impairment or optimisation of any saccade characteristic such as velocity and latency, or there may be a tradeoff between them.

The results of the previous studies yielded inconsistent results for the effects of mental workload on saccades. Some studies found an increase in the level of cognitive workload and visual demand can be indicated by an increased saccade velocity (App & Debus, 1998; Di Stasi et al., 2009; Di Stasi, Marchitto, et al., 2010; Hirvonen et al., 2010; Di Stasi, Antoli, et al., 2011; Di Stasi, Contreras, et al., 2011; Di Stasi et al., 2012; Di Stasi et al., 2013). However, there are studies that found a decrease in the velocity of saccades when the mental workload and difficulty of a visually demanding task increased (May et al., 1990; Van Orden et al., 2001; Di Stasi, Renner, et al., 2010). Halliday and Carpenter (2010) used an antonym task in conjunction with a saccade task and found latency of prosaccades was influenced by the level of cognitive load imposed by the interfering task, but also was dependent on which task had priority of performance: the distracter or the saccade task. Since velocity and latency of prosaccades can be
influenced by such internal states and task demands, we hypothesised that the effects of both task demands and internal states on the latency of saccades may contribute to the change in target acquisition time.

A tradeoff between speed and accuracy in a saccade task has been found to affect the latency of saccades (Reddi & Carpenter, 2000; Flehmig, Steinborn, Westhoff & Langner, 2010; Salvia et al., 2013). The accuracy of visual tasks has been found to be related to both saccade latency (Van Stockum et al., 2011), and target acquisition time (Recarte & Nunes, 2003). Secondary saccades can contribute to target acquisition time and final end point position (Toyomura & Omori, 2003). A concurrent discrimination task with a saccade task has resulted in not only a reduction in saccade latency (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005; Guyader, Malsert & Marendaz, 2010; Van Stockum et al., 2011), but also an increase in the number of secondary saccades used to position the eye on the desired target (Kapoula & Robinson, 1986). This chapter argues that as target acquisition time can be longer, possibly due to delayed saccade execution, changes in saccade latency can stand as an indicator of mental load and task performance. We also hypothesised that the generation of secondary saccades can be affected by mental load.

The results of this study will provide more information about the effects of cognitive tasks on saccades when overlapping attentional fields of both mental task and visual demand. The findings can also be useful in the context of work safety and task performance with a high workload. If the experimental protocol used in this chapter can induce cognitive stress in normal subjects, we can use the same task condition to induce stress in the group of subjects with infantile nystagmus.

2. Method

We have conducted acuity and saccade experiments in a group of normal subjects, as explained below in more detail. It is worth noting that the results of the “acuity experiment” were used to ascertain that the current experimental protocol can induce cognitive stress and high mental workload within subjects. We then used similar tasks to induce high mental workload in a
group of participants with INS. The details for the experiments in the INS group will be described in the next chapter.

2.1. Participants

Thirty-two students from the University of Melbourne (24 female and 8 male, mean age ± SD: 30.81 ± 12.5 years) volunteered to attend in saccade experiment 1 and the acuity experiment. An additional group of 7 participants (5 female and 2 male, mean age ± SD: 28.75 ± 12.3 years) also attended in saccade experiment 2, which was a modified version of saccade experiment 1. Participants who attended in saccade experiment 2 were not included in any other experiment. Except for one female and one male who attended saccade experiment 2, all the other participants were students.

During a short screening interview, all participants were determined to have no prior history of neurological diseases, ocular abnormalities, sleep disorders, psychiatric conditions, or drug abuse. All participants were free of medications and drugs. None of the participants consumed alcohol the night before the test. The participants were asked to avoid consuming caffeine for a minimum of four hours before the tests. A screening test by an examiner prior to the experiment ensured there was no presence of ocular tropia, or visual acuity of less than 6/9 in either monocular or binocular viewing. This involved cover tests and measuring visual acuity using a Snellen chart located at approximately 160cm away from the participant. To meet the criteria for visual acuity, a third of the participants wore their eyeglasses during the experiment. Participants were naive to the experimental aims and were requested to not consume alcohol the night before the session. All participants were provided with an information sheet and gave informed consent, approved by the Human Ethics Committee of the University of Melbourne (HREC # 1034131.2) prior to participation in the experiments outlined below.

2.2. Procedures

All procedures contributing to this study were approved by the University of Melbourne Human Research Ethics committee.
Head referenced eye movement recordings were done for both horizontal and vertical eye movements across ± 25° gaze positions with 5° steps from centre during a calibration run (baseline task), and during the tasks undertaken specified for the acuity and saccade experiments. For saccade experiment 1, participants were required to undertake another three tasks, including triple-, dual- and single-tasks which varied in task difficulty and level of induced mental load. Our procedure for the acuity experiment was similar to the experiment conducted by Cham et al. (2008b) and consisted of a baseline task and a visual discrimination task under both an unrestricted viewing time condition and a restricted viewing time condition with mental arithmetic.

All experiments were performed in one session, with a minimum of 1 minute between all tasks. There was an additional break allowed between acuity and saccade experiments that varied from 2 to 15 minutes. During that time, the headband of the eye tracker was sometimes removed or slipped off the head. This required the examiner to repeat the eye tracker calibration and baseline task before the acuity tasks started. Hence, the procedure for each acuity and saccade experiment consisted of four parts in this order: EyeLink II calibration, a baseline task, and the tasks related to saccade experiment or acuity experiment. Each part of the experimental procedure is described later in the following sections.

All tasks were presented with a projector onto a screen located at a distance of 1.6m directly in front of the participants. Before the tasks started, the eye tracker was calibrated for each eye. Then, binocular recordings were done for both horizontal and vertical eye movements during experimental tasks. Only horizontal eye movements were analysed (see data analyses section). Pupil size, skin conductance level, pulse transducer and infrared plethysmograph to measure heart rate and subjects’ task performance (the time and accuracy of manual responses) were also used to monitor the level of subjects’ mental stress during each task. The subjective measurement of mental workload was done separately for each task condition at the end of the acuity tasks and before measurement of resting levels for heart rate and skin conductance level. The resting levels used for heart rate and skin conductance level were the same as the measurements used in both experiments. We wish to note that the resting level condition was to ensure a low level of mental stress or arousal induced during the calibration (baseline) task. The details of the procedures and tasks have been explained below.
2.2.1. **Calibrating of eye tracker**

We used an EyeLink II high-speed head mounted video eye tracker (SR Research, Mississauga, Ontario, Canada) at a sampling rate of 500 Hz in pupil tracking mode to simultaneously record head-referenced eye movements, and pupil size. The eye tracker needed to be calibrated before the beginning of the data collection. This was done for each eye separately with the other eye was patched. We set up EyeLink II calibration using nine horizontal and vertical fixation points (HV9), and valid fixation duration set for a minimum of 1000 msec. For each presented point, the EyeLink II marked a valid fixation point on the EyeLink II host computer. The examiner then manually accepted each marked point until a reasonably symmetric cross pattern for the calibration grid was displayed on the screen of the EyeLink II host computer. We accepted the calibration run if the accuracy of the recording, displayed on the host computer monitor, was ≤0.5°. The precision of the eye tracker for horizontal and vertical amplitudes was 0.05°. After this initial calibration of the eye position, we scaled data off-line for each eye using the baseline task explained below.

2.2.2. **Baseline task (Calibration run)**

During the baseline task, subjects were required to fixate on a 0.3° square fixation target presented horizontally across ± 25° with 5° steps separations from the centre. Each gaze position was tested twice, i.e., from right to left and then vice versa, whilst each presentation lasted for 5 sec.

Baseline task (calibration) was carried out monocularly for each eye with the other eye patched. The baseline task was carried out to scale off-line the horizontal eye position for each eye; that aimed to convert the scale of horizontal eye position from pixels to degrees. Calibration was repeated for each individual eye when required, as in such cases where the headband of the eye tracker was removed between tasks. The method used to scale off-line horizontal eye position will be explained in section 3.2 of the data preparation.

2.2.3. **Saccade experiment 1**

Participants were required to fixate on the 0.3° square shaped fixation target until it randomly disappeared after 1.5-3.0 sec followed by a tumbling E target presented randomly across ± 25°
eccentric gaze positions (horizontally) with 5° steps from the centre. The size of the eccentric targets was the same as the size of the central fixation target. Participants were required to fixate on the tumbling E and manually identify the direction with their right hand using right or left keys on a game player console. The target disappeared 100 msec after the subjects’ manual response, or if no response was given, in 1 sec. The E target was followed by the central fixation point, and participants were required to look back at it until a new E target appeared at a random time and position. Each task contained 101 trials starting with the central fixation point, and each eccentric location was tested 5 times.

The task was repeated under three conditions including single, dual, and restricted triple conditions. For the restricted triple condition, participants were required to perform the task while simultaneously doing verbalised mental arithmetic. They had to continuously subtract 7 from a given number between 100 and 150, which was randomly chosen by the experimenter. In contrast with the triple task, in which the response time was limited to 1 sec, the response time was not limited for the dual task condition. Also, participants were not required to do mental arithmetic during dual task condition. Prompt manual responses were encouraged in both dual and triple tasks, more specifically during triple task condition.

During the single task, no mental arithmetic or manual response was required. Each target was presented for 1 sec at eccentric positions. The eccentric targets were not acuity demanding and were the same as the fixation point used at return trials (the trials to present the central fixation point).

2.2.4. Saccade experiment 2

As we will explain in a further section for the method of analysing data, we also used the LATER model of latency distribution to investigate the effect of mental load on saccade latency. We will explain in the results section that we found a significant difference between task conditions in latency of saccades. Thus, we decided to use the LATER model to investigate the source of those changes in latency (explained further in data analyses section). To make sure that the limited number of trials did not affect the fitted distribution lines in the LATER model analysis of saccade latency, saccade experiment 1 was repeated in a new group of participants after it was modified to include a larger number of trials. We have named the modified
experiment, “saccade experiment 2” during which each eccentric gaze position was tested 15 times, resulting in the number of target trials increasing from 50 to 150. We were interested only in analysing saccade latency data using the LATER model in the saccade experiment 2. Therefore, except for saccade latency, no other information was included in data analyses for saccade experiment 2 (see the section of data analyses). More details for analyses of latency data by the LATER model have been explained later in section 3.4.

2.2.5. **Acuity experiment**

Using Tumbling-E targets, the acuity tasks were presented in descending sizes using SR Research Experiment Builder 1.6.2. Due to limitations of screen resolution and distance of the stimulus from the subject (1.6m), acuity sizes were limited to approximately 1.8, 1.75, 1.7, 1.65, 1.6, 1.5, 1.4, 1.3, 1.1 and 1 logarithm of minimum angle of resolution (Log MAR). To compensate for the limited range of target sizes which could be presented, and to ensure that recognition difficulty could be maintained even for the participants with good acuity, the contrast of the acuity targets was also reduced. Contrast was defined as the difference between the luminance of the acuity target and the screen background divided by the background luminance (\( \frac{L_{\text{target}} - L_{\text{background}}}{L_{\text{background}}} \)). To vary contrast, grayscale levels of the acuity targets were varied while the background was kept white at all times. For a displayed target on a screen, contrast is affected by factors such as the characteristics of the screen and the lighting conditions (Metha, Vingrys & Badcock, 1993; Sharma, 2002; Shiiba et al., 2010). To overcome these influencing factors, the luminance was measured for the various grey levels displayed on the projector screen using a PR-650 SpectraScan Colorimeter photometer. The measurements were done randomly at different times of the day including morning, afternoon, and evening since the computer might have been used by other people for various durations each day. We then plotted luminance measures versus grayscale values (Figure 10). That indicated that Tumbling-E targets could be presented on the screen background with contrasts of 98%, 51%, 25%, 10%, 5% and 2%, approximately. Mean ± standard deviation (SD) of the maximum and minimum luminance of the projected image was measured to be 86.8 ± 3.8 candela/m² and 1.6±0.4 candela/m², respectively. Only horizontally oriented targets were used because we aimed to use the same task for the participants with nystagmus (Wilson, Mets, Nagy & Kressel, 1988). More details for the experiments in nystagmus group have been provided in the next chapter.
The task was started from 1.65 log MAR acuity size with a contrast of 50%. Participants were required to respond to the direction of the E targets facing randomly to the right or left by pressing right or left keys of the SR Research game controller. Participants were asked to guess the response if they were unsure about the direction of any E target. Two correct responses or one incorrect response at each size step were followed by a 2 step decrease in size or a 1 step increase in size, respectively. The contrast level of the acuity targets increased by 1 step if participants failed to respond correctly to the largest target at a given contrast level. If participants were able to respond correctly to the smallest target at a given contrast level, the test continued with the presentation of another E-target with 1 step lower contrast but 2 steps larger in size. The experiment was terminated if participants could identify the smallest size with the lowest contrast (size 1 log MAR with 2% contrast), or could not detect the largest size with the highest contrast (size 1.8 log MAR with 100% contrast), or after 4 reversal responses at any contrast level. The count of reversal responses was reset to zero whenever the contrast level changed.

Similar to the experiment by Cham et al. (2008b), participants were required to do the task under two conditions: an unrestricted single viewing condition, and a restricted dual task
condition. For the single viewing condition, participants’ responses were not time limited, and a response to the acuity target was required for the next target to be presented. If the participant thought no target had been presented, the examiner asked him/her to make a forced choice response i.e., guess the response or press any key randomly, in order to meet the condition for the end of the trial. Participants’ manual response to each acuity target was followed by a fixation cross (Figure 11a). For the restricted dual task condition, each target was presented for 0.5 sec followed by a visual noise mask for 300 msec. A manual response to the optotype target could only be submitted during viewing of a fixation cross presented for 1 sec (Figure 1b). A noise mask in the restricted dual task condition obscured possible afterimages of the target optotype, as it was during this task that a persistent afterimage could have provided uncontrolled additional time in which the target could be viewed. Participants were also required to do the task simultaneously with verbalised mental arithmetic (continuously subtracting 7 from a number selected randomly from 100-120, given by the examiner during the task). The program treated any three consecutive missed responses as one incorrect response. To keep the participants at a high acuity demanding level for an extended period of time, the number of reversal responses increased to 6 in the restricted dual task.

Figure 11: A schematic diagram showing the unrestricted single task (a) and the restricted dual task (b).
It is worth noting that the current experiment, despite being similar in design to low contrast acuity tests such as Sloan charts, was not capable of measuring clinical visual acuity or contrast sensitivity. Instead, we aimed to present a visual discrimination task with reduced target visibility. Since our hardware was not able to present sufficiently small optotypes, visual demand was also increased by reducing stimulus contrast.

2.2.6. **Common considerations**

Prompt manual responses were encouraged for both the saccade and acuity experiments. Participants could also be alerted to their performance by the examiner if there were frequently missed manual responses or delayed verbal arithmetic (>5 sec). For the tasks in which concurrent mental arithmetic was required, the participant’s voice was recorded to monitor performance (with consent of the participant). The time of the recording was not synchronised with the other recordings such as heart rate, and the voice-recording file was discarded after being reviewed by the examiner on the same day. All tasks were done with optical correction (if habitually required) and in dim room light. To minimize the influence of environmental factors including heat and noise on physiological measurements, testing conditions in the laboratory were kept as consistent as possible.

Physiological measurements were used to determine variations in task conditions using pupil size, blood volume pulse waveforms, and skin conductance level (SCL). Baseline measures for INS parameters, pupil size, heart rate, and skin conductance level were recorded during calibration runs; more details for data analyses in INS group have been provided later in the next chapter. To ensure that possible stress or arousal due to discomfort with the lab environment did not influence baseline values, we recorded heart rate and skin conductance level at the end of the tasks as the resting condition. Before the resting level was recorded, participants were asked to stay seated and to relax for 10 minutes. Then, we recorded heart rate for 6 minutes. The participants were asked to not do anything and to sit at rest while looking straight at the standard blue Windows XP screen. The measures obtained for the last 4 minutes of the resting condition were compared with the baseline measures; the length of this period was similar to that of the baseline condition. Allowing 12 minutes for post-stress recovery let participants return to a state
of relaxation after the tasks were completed, and minimised post-stress effects on the measurements obtained as resting level (Earle, Linden & Weinberg, 1999; Kudielka, Buske-Kirschbaum, Hellhammer & Kirschbaum, 2004). The heart rate and skin conductance level obtained as the resting level was compared with the baseline measures to confirm the absence of stress or heightened arousal during the baseline condition.

Head movements were minimised during all tasks with an adjustable supportive headrest. Moreover, head position was also monitored by recording the positions of the head markers of the EyeLink II (explained in detail in section 3.3).

2.3. Apparatus

The experiment was programmed using SR Research Experiment Builder 1.6.2. Head-referenced eye movements and pupil size were recorded using an EyeLink II eye tracker, as described in section 2.2.1.

All visual targets were presented with a 1024 × 728 NEC-WT610 projector with a photocell in a corner of the screen being used to index the onset and offset time of each target. Using the analogue output from the EyeLink II (resampled at 1000 Hz) allowed us to synchronize the time of the eye movements with the target timing. The digital output from EyeLink II was used for the analysis of eye position in MATLAB R2012a (The Mathworks, Natick, MA) after being digitally low-pass filtered with a cutoff at 70Hz. A bidirectional filter (using the Matlab filtfilt command) was applied to the data to avoid time delays. The filter used a mean squares algorithm to produce the least error signal; i.e., the difference between the desired and the actual signal. Velocity data were derived from the position data and smoothed using a second order differentiator with a cutoff frequency of 62.5Hz.

Skin conductance level and blood volume pulse waveforms were recorded simultaneously with pupil size and eye movement recordings. Skin conductance level and heart rate were recorded using non-invasive AD Instruments MLT116F GSR finger electrodes and MLT1020EC plethysmograph ear clip transducer, respectively. The finger electrodes were attached to the middle and ring fingers of each participant’s left hand. Artifacts induced by physical movements.
were monitored by a piezo-electric pulse transducer (MLT1010) attached to each participant’s left thumb and affected data were excluded from analysis. Participants were asked to steadily rest their left hand on the armchair. All participants were right handed. It is worth noting that all of the participants were right handed.

The subjective workload was measured using a computer version of NASA-TLX (National Aeronautics and Space Administration Task Load Index), purchased from http://humansystems.arc.nasa.gov/groups/TLX/index.html. NASA-TLX is a multi-dimensional rating procedure that derives an overall workload score based on ratings on different subscales (Hart & Staveland, 1988; Moroney, Biers, Eggemeier & Mitchell, 1992, May; Moroney, Biers & Eggemeier, 1995; Hart, 2006). For each participant, a subjective measurement of the mental workload was done at each task condition by the mean of the mental, temporal and effort subscales (MTE). The MTE score was calculated as the average of the rating scores for mental demand, temporal demand and effort subscales from the NASA-TLX, within 15 minutes after each task (Hart & Staveland, 1988; Moroney et al., 1992, May; Moroney et al., 1995; Hart, 2006).

3. Data preparation

Subjects were excluded from data analyses if they frequently took more than 5 sec to give consecutive arithmetic responses. All data collected for eye movements and physiological measurements of mental load were analysed off-line after the experimental procedures were completed; the details are provided below.

3.1. Physiological measurements of mental load

3.1.1. Heart rate and skin conductance level

The data collected for skin conductance level and heart rate were exported to MATLAB R2012a. Subjects’ data were not included in the analysis if the pulse transducer recordings showed unacceptable noise, presumably due to major physical movements. Mean skin conductance level was calculated for each task condition within subjects. The timing of peaks in
blood volume pulse (BVP) signals were determined. Then, the timings imported into Kubios HRV Version 2 (Free download available at http://kubios.uku.fi/KubiosHRV/Download/) that was used to calculate heart rate as the number of beats per minute (bpm).

### 3.1.2. Pupil size

The pupil size data collected by Eye Link II are in arbitrary units. Measuring pupil area is based on the number of pixels of the thresholded area in the camera image, i.e., the coloured area in blue when the participant is being set up before eye tracker calibration. The pupil measurements are highly variable across subjects, being dependent upon factors including face structure and the distance between a participant’s eyes and the eye tracker cameras. According to manufacturer’s forum of SR Research, the eye tracker does not provide vertical and horizontal diameters of the pupil. Due to the above characteristics of the eye tracker for measuring pupil size, we measured percent change in pupil area from a baseline value, explained below in details, separately for each individual subject. Thus, the within-subjects nature of the analysis should minimise the effects of these individual differences.

Because the system software did not correct for the image of the pupil becoming more elliptical in lateral gaze, pupil size was measured only during foveation at each task condition and gaze position. Since dilation was expected with increasing workload, it was important that this not be masked by the apparent reduction in the area which an elliptical image would cause. Using EyeLink Data Viewer software (SR Research, Mississauga, Ontario, Canada), the mean pupil area during fixation periods on the desired visual target was exported for each trial. Fixation losses due to saccades larger than one degree were not included in the analysis. Fixation periods followed by or preceding blinks were excluded from data analyses. Pupil size was averaged across the selected fixation periods, separately for each gaze position and task condition within subjects. The change in pupil size from baseline was then measured for each task condition, both within subjects and within gaze positions.
3.2. Re-scaling horizontal eye position (off-line calibration)

An interactive MATLAB program plotted a target marker, the horizontal eye positions and velocity data recorded at the calibration run (baseline task), versus time. For each target location, the examiner selected by a mouse click the data points of eye positions where foveation of the target occurred. The examiner selected the potential foveations based on the velocity trace while the eye positions were similar for the same target locations. For normal participants discussed in this chapter, the target of interest was typically foveated at the end of saccade(s) towards it. The program then plotted the selected points versus target locations. The examiner repeated this process to identify foveation locations across the range of gaze positions and then calculated the linear regression line that best fit the data. The resulting line was then used to scale the other data, i.e., eye position and velocity used in the study.

Using the linear regression line, the eye that was better calibrated was selected for the study. If the right and left eye showed similar calibration quality, the examiner selected the right eye to test. For participants with nystagmus, in the case of similar calibration quality between eyes, the eye with better visual acuity at primary gaze position was selected to test. This has been explained in the next chapter.

3.3. Measuring eye movement variables

At the end of the experiments, the positions of the head markers were plotted versus time. The resulting graph was used to qualitatively evaluate whether the participants moved their head during each task. If the participant’s head position looked to be unstable, those recordings were excluded from analysis. Moreover, the examiner used off-line calibration to exclude the gaze positions in which the participant’s head appeared to move. It is worth noting that EyeLink II does not provide quantitative data for the subjects’ head movements. No data were excluded from the normal subjects due to head movements. For INS subjects, 4.06 ± 2.73 (mean ±SD) out of 11 gaze positions were excluded from analyses of the acuity experiment due to subjects’ head movements. Thus, analyses of INS parameters were limited to only the null and 15° away from it, as explained in chapter 4, section 4.
In this section, we first describe how data were processed for each eye movement variable. Then, the statistical analysis to investigate each variable across task condition will be explained.

### 3.3.1. **Initial saccades**

Saccades were selected using a custom written program in MATLAB that presented potential saccades for manual review and selection. The MATLAB program used the criteria 10 °/s and 8000 °/s² for saccade onset and offset after target step. Potential saccades selected by the program were reviewed manually, limiting the selection to initial saccades during which fixation was disengaged from the initial target location and the eye accelerated towards the new target position.

Latency, gain, duration, and peak velocity were measured for each initial saccade at each trial. Trials with blinks associated with the saccade were not included in the data analyses. Saccade gain was defined as the amplitude of the saccade divided by the amplitude of the target step. Latency was defined as the time between target presentation at the new position and saccade onset. Trials with anticipatory saccades or inaccurate saccades were also not included in the analysis. Anticipatory saccades have been described as saccades with latency less than 80 msec (Fischer & Ramsperger, 1984, 1986) and were excluded from data analyses. We defined inaccurate saccades as the saccades with gain of less than 0.5 or greater than 1.5 (Bieg, Bresciani, Bülthoff & Chuang, 2012), or initial saccades with directional errors (the primary saccade was not directed towards the target, such as when a participant looked up to think).

Using GraphPad Prism Version 5 for windows (GraphPad Software, La Jolla, CA), asymptotic peak velocity (Vmax) and its constant k were estimated for each subject by fitting a saturating exponential of the form peak velocity=Vmax (1-e^{-amplitude/k}) to a plot of peak velocity versus amplitude (the “main sequence” plot). The average gain of the saccades was calculated separately for each participant, task condition (single, dual, and triple), and type of trial (i.e., saccades toward eccentric targets during target-trials and saccades toward the central fixation point during centre-trials (return-trials). For latency, both mean and median were calculated for each task and type of trial within subjects.

The proportion of each type of saccade (express, fast regular, and regular) was calculated for each task. Express saccades were defined as initial saccades with latency shorter than 130 msec but larger than 80 msec. The saccades with a latency of 130-200 msec were classed as fast
regular saccades, while saccades with latency longer than 200 msec were classed as regular saccades (Boch & Fischer, 1986; Fischer & Ramsperger, 1986; Inhoff, Topolski, Vitu & O’Regan, 1993).

3.3.2. **Secondary saccades**

Using the same velocity criteria utilised for initial saccades, the secondary saccades following them were also identified and analysed. Secondary saccades were defined as corrective saccades following initial saccades and directed at the target of interest. Like initial saccades, secondary saccades that were identified by the MATLAB program were reviewed and selected manually. The ratio of secondary saccades was calculated within subjects as the number of secondary saccades divided by the number of initial saccades for the same trial type and task condition. The latency of the secondary saccade was calculated as the time between the end of the primary saccade and the onset of the subsequent secondary saccade. The gain of the secondary saccade was defined as the amplitude of the secondary saccade divided by the amplitude of the target step. Similar to the initial saccades, any effect of the task on the gain and latency of the secondary saccades was investigated within subjects. Velocity was not included in the data analyses for secondary saccades.

3.3.3. **Final saccadic end position**

For each trial, final saccadic end position was calculated as the sum of the amplitudes of the initial and secondary saccades recorded at the same trial. For a trial with no secondary saccade, final saccadic end position was the same as the amplitude of the initial saccade. The error in the accuracy of final saccadic end position was measured as the absolute magnitude of the remaining error. It is worth noting that we did not examine final saccadic end position for INS group, as explained in the following chapters.

3.3.4. **Target acquisition time**

Target acquisition was determined manually by moving a cursor in the interactive window to the point where the eye reached the target of interest. This position was not necessarily identical
to the new target position, but was usually close to the final saccadic end position, or where the trace of eye position remained fairly stable, within ±0.5° of the desired target. Target acquisition time was calculated for each trial as the time taken for the eye to reach the target after target onset. Figure 12 shows a diagram for measuring saccade latency, final saccadic end position, and target acquisition time. For all of the illustrations in the current thesis, up indicates right and down indicates left to the central gaze position.

3.1. Using LATER model to analyse latency data

Although changes in the mean or median of saccade latency can reflect the extent to which our task conditions can influence the decision time required for saccade generation (Hutton, 2008), the source of the changes in latency remained unclear. For example, there is a possibility that our participants voluntarily changed the criterion level of the tasks (e.g., a higher priority for the arithmetic task rather than the saccade task or vice versa) while they might not have worried about their performance in the other one. This possible choice could have been investigated using the LATER model (Reddi et al., 2003). Based on the LATER model, changes in latency of

![Figure 12: Schematic illustration of eye movement recording from a normal subject. Time of stimulus onset in a new position (a), start of the target-acquiring saccade (b), end of the initial saccade towards target (c), start of the secondary saccade (d), and the final saccadic end position at the time of target acquisition (e), are displayed for illustration purposes.](image-url)
saccades could be due to the changes in the parameters contributing to the speed of saccade generation, including initial level, execution threshold, or rate of rise in saccade decision signal (Carpenter, 1981; Carpenter & Williams, 1995). Changes in the cognitive process can have a differential effect on parameters of the LATER model analysis of saccade latency (Carpenter, 1981; Carpenter & Williams, 1995). Knowing the effectiveness of distribution modeling in the analysis of reaction times, we investigated the latency of saccades towards eccentric targets using LATER model parameters for saccade tasks. A greater number of trials in saccade experiment 2 than saccade experiment 1 could allow a better fitted distribution line for latency data. We investigated to what extent task condition affects parameters of the LATER model, as was explained in detail in the previous chapter. To accomplish this, we used SPIC software that is free to download from http://www.cudos.ac.uk/spic.html.

Using the reciprobit plots explained in the LATER model, the mean rate of rise in the saccade decision signal (µ-value) was calculated for each participant across task conditions for target trials. As explained in the previous chapter, the factors influencing saccade latency could have selectively swiveled or shifted the best fitted line in the LATER model. Using three task conditions, the log likelihood ratio (LLR) of shift versus swivel tested the probability of the best fitted line for any effect of task condition for each participant. Shift was favoured over swivel if a negative number was obtained for the ratio of log likelihood (LLR<0) and vice versa. The values of LLR were then summed across participants to examine the general effect of task condition on the type of fit. An overall shift effect could be observed if the sum (Σ LLR) was positive, while a negative number could show a swivel effect of task condition on saccade latency. At the next step, the general fit determined by Σ LLR (fixed slope in the case of a shift effect or fixed intercept in the case of a swivel effect) applied for each participant. Using the general fit (that was a shift for our data), µ-value was recorded for each task condition and participant while the amount of σ was fixed across the task conditions.
4. **Statistical tests**

The analyses were conducted on the collected data using IBM SPSS Version 20 (IBM Corporation, Somers, NY). We also used GraphPad Prism version 5.0 for Windows to illustrate our results. The Kolmogorov-Smirnov test was used to investigate normality of data distributions. For normally distributed data, there was insufficient evidence to reject the assumption of homogeneity of variance. We then conducted one-way and two-way ANOVA procedures for repeated measures (details are explained in following sections). For each ANOVA, main effects and interactions were examined. Means and standard errors of the means (mean±SEM) were calculated for each factor combination, and comparisons were conducted between pairs of factor levels. Plots of means for each pair of factors were constructed to help assess interactions. In cases where sphericity could not be assumed, Greenhouse-Geisser corrections were used. If the results obtained by repeated measures ANOVAs showed a significant effect for an experimental condition, the results between pairs of within subjects factors were compared using post-hoc paired t-tests or the equivalent non-parametric tests. Bonferroni correction for multiple comparisons was used to adjust the p-values. For a dependent variable, the statistical results of the post-hoc tests were reported as the mean±SEM of the within-subjects’ differences between desired conditions, followed by statistical results for the comparisons. We have explained the details of each statistical test used for each variable in the following sections.

We wish to note that we were interested only in latency data in saccade experiment 2. Except for the LATER model distribution of saccade latency, no other saccade characteristics or physiological measures were included in the analysis for participants in saccade experiment 2. We therefore mean saccade experiment 1 when we refer to the “saccade experiment.”

4.1. **Workload measurements**

In each saccade and acuity experiment, a one-way ANOVA for repeated measures tested the effect of task on heart rate, skin conductance level, and MTE score of subjective mental workload measurement. Task was considered as a factor within subjects to investigate the level of mental workload and consisted of three levels being single, dual, and restricted triple tasks in
the saccade experiment. Tasks for the acuity experiment included baseline, unrestricted single
task, and restricted dual task.

Conducting paired t-tests between resting level and baseline data confirmed that the level of
the mental load during baseline was low. Subjective measurement of mental workload, heart rate,
and skin conductance level were also examined for any effect of participants’ gender using the
group-wise comparison of one-way ANOVA for repeated measures.

At each task condition, a paired t-test was used to reject the possibility of a significant
difference in pupil size between right and left gaze positions. Pupil data were then averaged
between right and left gaze positions after the similarity between right and left sides was
confirmed. Since dilation was expected with increasing workload, it was important that this was
not masked by the apparent reduction in the pupil area that an elliptical image would cause.
Separate measurements of change in pupil area were then made at each of the gaze positions
from baseline for each task. The baseline for each gaze was the value measured at the same gaze
position used in the calibration run. Two-way ANOVA for repeated measures investigated the
effects of gaze position and task condition on the change in pupil size from baseline.

4.2. Task performance

4.2.1. Acuity experiment

Task performance was defined for each acuity task and gaze position as the contrast and size
of the last optotype which was correctly identified by the participant. All participants reached 2%
contrast across all tasks and gaze positions. Thus, the analysis was conducted for variable size
only. For each task, the average LogMAR size (logarithm of minimum angle of resolution)
between right and left gaze was considered for analysis after a Wilcoxon Signed Ranks Test
showed no significant difference between them. Using statistical software environment R and the
package nparLD (Noguchi, Gel, Brunner & Konietschke, 2012), a rank-based ANOVA-type test
(Brunner, Munzel & Puri, 1999) investigated any effect of task and gaze positions on variable
size. Only the central gaze position and ±15° were included in data analyses due to the
limitations of available data in INS subjects. This is explained in the next chapter.
4.2.2. **Saccade experiment**

The effect of task on performance was investigated. The variables of task performance were visual processing time, the subject’s reaction time (manual response time), and the accuracy of the subject’s response errors in the post-saccade discrimination task. Each variable was calculated for each saccade task within subjects. A subject’s reaction time was measured at each trial as the time between onset of the visual target on screen, determined by the analogue output of the photocell installed at the corner of the screen, and the time when the subject responded to the target (i.e., identified the direction of the E target as being right or left). Visual processing time was calculated from target acquisition time until the subject submitted a response for the post-saccade discrimination task. The ratio of the subject’s response errors was defined as the number of incorrect or lapsed responses (>1 sec) divided by the number of required responses.

Each measure of task performance was averaged across gaze positions and then investigated for any effect of task condition within subjects. Paired t-tests compared visual processing time and subjects’ reaction time between dual- and triple-task conditions. The non-parametric Wilcoxon Signed Rank Test for two related samples tested response accuracy for significant differences between tasks. As the Kolmogorov-Smirnov test failed to show normality of manual response time only for the dual task (p=0.002), the results of manual response time were checked with the Wilcoxon Signed Rank Test.

4.3. **Eye movement variables**

Characteristics of saccades were analysed for main effects of task and type of trial using a two-way ANOVA for repeated measurements (3 tasks × 2 trial types). Similarly, target acquisition time, final saccadic end position, and absolute magnitude of the remaining error were all investigated for effects of task and trial type.

The change in different kinds of saccades used to get on the target was investigated for any effect of the task within subjects. That included express, fast regular and regular saccades for initial saccades, and ratio of secondary saccades. Section 5.3.1.3 will provide details for analysis of saccade categories.

Pearson correlation investigated any significant association between mental load (i.e., MTE score, heart rate, skin conductance level) and measures of eye movement reaction time i.e.,
target acquisition time and saccade latency). Spearman correlation also was used to investigate to what extent task performance was associated with the ratio of secondary saccades, target acquisition time, and final saccadic end position.

In addition to the ratio of log likelihood obtained for participants, one-way repeated measures ANOVA tested for any effect of task on the $\mu$-value of saccade latency. A non-parametric Wilcoxon Signed Ranks Test for related samples was used to compare $\mu$-values obtained for the latency of manual responses between tasks.

5. Results

Among thirty-two participants, one was excluded from the analysis of physiological measurements and eye tracking during the acuity experiment due to a failure in the hardware. Only the data for task performance could be analysed for this participant. One participant withdrew from the acuity experiment after she took part in saccade experiment 1. Two participants were excluded from the analysis of saccade experiment 1 due to poor performance, including excessive blinks and lapsed manual responses even in the task without arithmetic. None of the participants were excluded from analysis due to lapses in the arithmetic task when voice recordings were reviewed by the examiner. The results for workload indicators, task performance and eye movement data are explained below for each experiment.

5.1. Workload indicators

A paired t-test showed no significant difference between baseline condition and resting condition for skin conductance level ($p>0.2$). However, paired t-tests for heart rate showed a significant decrement at rest when compared to the calibration task (mean difference $\pm$ SEM: $-2.94 \pm 0.80$ bpm; 95% confidence interval [CI]: $-4.61, -1.27$; $t_{25} = -3.639$, $p=0.001$).

Group comparisons of the repeated measures ANOVAs showed no significant difference between gender groups for the changes in MTE score, heart rate (HR), and skin conductance level (SCL) from baseline with no interaction with task ($p>0.5$). Thus, the statistical tests explained in the current and following chapters, i.e. chapters 3-4, did not include any statistical
test for between-groups comparisons and independent samples t-tests. Below we have compared three task conditions of the acuity experiment and saccade experiment, including calibration task (baseline), the task with mental arithmetic and time restriction, and the task without mental arithmetic and time restriction.

5.1.1. **Acuity experiment**

Figure 13 shows subjective and physiological measurements of workload across task conditions. For all subsequent figures, unless otherwise specified, error bars indicate standard errors of the mean.

For each task condition, paired t-tests did not show any significant difference between +15° and -15° gaze positions for pupil size (p>0.2). Change in pupil size from baseline was averaged between right and left gaze positions and investigated for any effect of task and gaze position. Two-way ANOVA for repeated measures tested any significant main effects of gaze position and task on pupil dilation from baseline. The results showed no significant main effect for gaze position on pupil dilation from baseline (p>0.07). Task significantly influenced %pupil dilation from baseline, which increased more for the task with arithmetic than for the task without arithmetic (14.496± 3.713; 6.79, 22.19; f_{1,22}= 15.241, p=0.001). There was a significant interaction between task and gaze position for %pupil dilation from baseline (f_{1,22}=5.971, p=0.023).

Task condition had significant effects on subjective MTE score (f_{2,48}=142.454, p<0.001). Post-hoc paired t-tests showed that subjective MTE score increased significantly during the restricted dual task as compared with baseline (70.75 ± 4.23; 59.81, 81.68; t_{24}= 16.649, p<0.001), and with unrestricted single task (48.85 ± 4.49; 37.29, 60.42; t_{30}=13.143, p<0.001). Also, the unrestricted single task showed a larger MTE score than the baseline task (21.89 ± 4.12; 11.28, 32.50; t_{24}= 5.310, p<0.001).

Task condition had significant effects on heart rate (f_{2,41,3}=16.40, p<0.001). Post-hoc paired t-tests yielded significantly higher heart rate during the restricted task than baseline (5.18 ± 1.02 bpm; 2.57, 7.79; t_{26}= 5.077, p<0.001), and the unrestricted task (6.108 ± 0.96 bpm; 3.63, 8.58; t_{30}=7.272, p<0.001).

Task condition had significant effects on skin conductance level (f_{1,32,34,21}=8.17, p=0.001). Skin conductance level significantly increased during the restricted dual task as compared with
baseline (4.04 ± 1.41 mhos; 0.42, 7.65; t_{26}=2.857, p=0.025), and the unrestricted task (3.49 ± 0.97 mhos; 1.01, 5.98; t_{27}=3.492, p=0.004).

Figure 13: Subjective MTE score (a) and physiological measurements of mental workload including heart rate (b), mean skin conductance level (c) and percent change in pupil size from baseline (d) across task conditions. Error bars indicate standard errors of the mean. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p < 0.0001; **0.001<p<0.01; *0.01<p<0.05.
5.1.2. **Saccade experiment**

Figure 14 shows changes in the physiological indicators of workload across saccadic tasks. Significant effects of the task were found for change in pupil size from baseline ($f_{1.267}=27.604$, $p<0.001$) with a significant interaction between the task and gaze position ($f_{5.432}=2.200$, $p=0.019$). There was a significant main effect of gaze position on pupil dilation from baseline ($f_{3.442}=23.249$, $p<0.001$).

![Figure 14: Subjective score (a), and physiological measurements of mental workload including heart rate (b), skin conductance level (c), and change in pupil size from baseline (d) across saccade tasks. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***$p<0.0001$; **$0.001<p<0.01$; *$0.01<p<0.05$.](image)
Task condition had significant effects on MTE score ($f_{1.32,34,21}=8.17, p=0.001$). MTE score significantly increased for the triple task compared to the single task ($19.92\pm1.25; 16.69, 23.14; t_{24}=15.308, p<0.001$), and dual task ($15.77\pm1.17; 12.77, 18.77; t_{26}=13.850, p<0.001$). A larger MTE score was measured for the dual versus single task ($4.14\pm0.82; 2.03, 6.26; t_{23}=4.796, p<0.001$).

Task condition had significant effects on SCL ($f_{1.32,34,21}=8.17, p=0.001$). Post-hoc paired t-tests compared tasks for any significant change in skin conductance level. The results showed that SCL significantly increased for the triple task when compared to the single task ($7.12\pm1.29$ mhos; $3.83, 10.41; t_{26}=2.857, p<0.001$), and the dual task ($2.40\pm0.82$ mhos; $0.31, 4.49; t_{27}=3.492, p=0.020$). Also, skin conductance level increased during the dual task as compared to the single task ($4.72\pm1.53$ mhos; $0.83, 8.61; t_{26}=0.708, p=0.013$).

Task condition had significant effects on heart rate ($f_{2,32,3}=12.462, p=0.001$). Post-hoc tests for heart rate yielded a significant increase during the triple task when compared to the single task ($9.45\pm2.67$ bpm; $2.58, 16.32; t_{25}=3.531, p=0.005$), and dual task ($10.25\pm1.17$ bpm; $7.25, 13.25; t_{25}=0.298, p<0.001$).

5.2. Task performance

5.2.1. Acuity experiment

As noted before, all participants showed a contrast level of 2% for the acuity thresholds measured during both restricted and unrestricted tasks across gaze positions. Wilcoxon Signed Ranks Test showed no significant difference between left and right gaze (-15° versus +15°) for the logMAR size of the last acuity target identified at restricted dual task, and unrestricted single task (P-values>0.1). The logMAR size of the last acuity target identified by participants was then averaged between right and left gaze and analyzed to investigate any main effect of task and gaze position (central gaze and ±15° away from centre). The results showed a significant increase in the size of the last acuity target identified by participants during the restricted condition as compared with the unrestricted condition (nparLD package; p=0.001). There was no main effect of gaze position. Gaze position and task condition had no interaction effect on task performance.
5.2.2. **Saccade experiment**

5.2.2.1. **Manual response time**

A paired t-test did not show any significant difference between the tasks for manual response time (for the dual task: 785.04±35.89 ms; for the triple task: 766.49±10.92 ms; p>0.57). As the Kolmogorov-Smirnov test failed to show normality of manual response time for the dual task (p=0.002), the data were also analysed with the Wilcoxon Signed Ranks Test (p>0.68).

5.2.2.2. **Visual processing time**

The Kolmogorov-Smirnov normality test showed normal distributions for visual processing times at both task conditions (p>0.07). A paired t-test did not show any significant difference between the tasks for visual processing time (for the dual task: 391.33 ± 40.36 ms; for the triple task: 348.29 ± 11.95 ms; p>0.27).

5.2.2.3. **Response accuracy**

Participants missed 23.85% of all required responses during the restricted triple task. The percent of response errors in the post-saccadic task significantly increased for the restricted triple task as compared with the unrestricted dual task (Overall, 10.8% in the triple task and 0.97% in dual task among participants; Wilcoxon Signed Ranks Test: p<0.001).

5.3. **Initial saccades**

Initial saccades, also known as primary saccades, were detected and analysed at both saccade experiments 1 and 2. Below, the results for these saccades have been explained separately for both saccade experiment 1 and saccade experiment 2. Any secondary saccades to correct the residual error of target acquisition were detected in saccade experiment 1 and will be discussed later.

5.3.1. **Saccade experiment 1**

Anticipatory saccades were identified in 0.1%, 0.4% and 0.5% of the trials, respectively for the single, dual, and triple tasks and were excluded from analysis. The characteristics of saccades
were investigated for any effect of task and trial type (target trials versus return trials) as discussed below. As described before, target trials refer to the trials that presented targets at eccentric locations and return trials (centre trials) refer to the trials with targets at centre, thus they returned the eyes back to the primary position.

5.3.1.1. Velocity and gain

Figure 15 shows the gain, asymptotic peak velocity (Vmax) and K-value across task conditions and trial types.

Velocity of saccade was significantly affected by target type only; i.e. the saccades made during return trials showed significantly larger Vmax and smaller k value than the saccades determined at target trials (for Vmax: 60.78±6.65 ○/sec; f\textsubscript{1,27}=83.47, \(p<0.001\); for K: 0.025±0.003; \(f\textsubscript{1,27}=78.43, \(p<0.001\)). ((-

The interaction between task and trial type was significant for saccade gain (\(f\textsubscript{2,50}=4.48, \(P=0.016\)). Target trials showed just significantly lower gain for the dual task when compared to single task (-0.017±0.007; \(t\textsubscript{27}=2.597, \(p=0.048\)) and when compared to triple task (-0.029±0.011; \(t\textsubscript{26}=2.630, \(p=0.042\)).

No other condition approached significance for the task or trial type (adjusted p-values>0.05).

3.1.1.1. Mean and median of saccade latency

Within-subjects’ data obtained for saccade latency typically do not have a normal distribution. Thus, we calculated both mean and median for each individual subject. The between-subjects’ data passed the test for normality, except for the median latency of return trials during the triple task. Hence, we conducted two-way ANOVA tests for repeated measures to investigate any effect of task and trial type on both median and mean of saccade latency.

Task condition significantly affected the mean of saccade latency (\(f\textsubscript{1,39,37.5}=22.887, \(p<0.001\)). Mean of saccade latency increased significantly for the triple task as compared with single task (35±7 ms; 18, 52; \(t\textsubscript{55}=5.980, \(p<0.001\)), and dual task (34±7 ms; 16, 52; \(t\textsubscript{55}=5.925, \(p<0.001\)). Task condition significantly affected the median of saccade latency (\(f\textsubscript{1,43,40.21}=14.50, \(P<0.001\)).
Median of saccade latency increased significantly for the triple task as compared with the single task (32.65±7.35 ms; 13.94, 51.36; t_{57}=5.067, p<0.001), and dual task (31.60±8.33 ms; 10.39, 52.82; t_{57}=4.446, p=0.002). The median of saccadic latency was also significantly affected by trial type; i.e. median of saccade latency was longer for target trials as compared with return trials (20.62±4.74 ms; 10.90, 30.34; f_{1,2}=18.897, p<0.001).

The Wilcoxon Signed Ranks Test obtained similar results for the median latency of saccades (restricted triple task versus unrestricted dual task: p=0.003; restricted triple task versus single
task: \( p=0.001 \)). No other condition approached significance. Figure 16-17 shows mean and median of saccade latency across tasks and trial types, respectively.

Figure 16: Mean latency of saccades across task conditions. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***\( p < 0.0001 \).

Figure 17: Median latency of saccades across task conditions. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***\( p < 0.0001 \).
3.1.1.2. Saccade categories

Figure 18 shows the latency and ratio of different types of saccades across task conditions and trial types. Kolmogorov-Smirnov tests showed normal distributions of data except for the ratio of express saccades across task conditions (all adjusted p-values<0.05). Because of insufficient residual degrees of freedom, producing multivariate test statistics was not possible for the latency of express saccades in target trials.

Nonparametric Friedman Test and Wilcoxon Signed Ranks Tests for related samples did not show any significant difference between tasks or trial types for the ratio of express saccades (p-values> 0.05). There were not enough valid cases to compute statistics for the latency of express saccades at target trials.

Two-way repeated measures ANOVAs tested any significant effect of task and trial type on ratio of saccade categories. Trial type significantly influenced the ratio of both fast regular saccades, and regular saccades; i.e. return trials showed more fast regular saccades (0.092± -0.020; 0.133, 0.052; $f_{1,28}=21.614, p<0.001$), and fewer regular saccades (-0.111± -0.022; -0.067, -0.155; $f_{1,28}=26.343, p<0.001$) as compared with target trials.

Also, task condition significantly affected the ratio of fast regular saccades ($f_{2,56}= 22.478$, p<0.001) and the ratio of regular saccades ($f_{2,56}= 25.191$, p<0.001). Post-hoc paired t-tests comparing the ratio of fast regular saccades in each task showed significantly fewer saccades during triple task as compared with the dual task (0.106±0.023; -0.164, -0.047; $t_{56}= 4.771$, p<0.001) and with single task (-0.130±0.020; -0.181, -0.080; $t_{57}=6.278$, p<0.001). Similar to fast regular saccades, the ratio of regular saccades increased for the triple task significantly, compared with dual task (0.110±0.025; 0.048, 0.173; $t_{57}=4.313$, p<0.001), and single task (0.146±0.020; 0.96, 0.197; $t_{57}=6.575$, p<0.001).
Figure 18: Latency and ratio of different types of saccades within subjects across tasks and trial types. Error bars indicate standard error from the mean. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p< 0.0001; **0.001<p< 0.01; *0.01<p<0.05.

Similar to the ratios for saccade categories, two-way ANOVA for repeated measures tested significant effects of task and trial type on latency of each saccade category. The results for fast
regular saccades showed significantly shorter saccade latency during return trials than during target trials (-3.687 ±1.127 ms; -6.00, -1.37; f_{1,26}=10.712, p=0.003).

No other significant difference was found between tasks or trial types.

3.1.1.3. LATER model results

Testing the swivel and shift with the best fitting line across three tasks showed a high probability of shift rather than swivel for both target trials (ΣLLR = -11.125) and return trials (ΣLLR = -8.563). Lines with the same fixed slope were fitted to the data points of saccade latency in the three tasks. Two-way ANOVA for repeated measures tested any significant effect of task and trial type on mean rate of rise in decision signal (μ). The results showed μ-value to be significantly affected by task conditions (f_{2,56}=13.674, p<0.001). Post-hoc paired t-tests compared μ-value between the tasks. The results showed the value of μ significantly decreased for the triple task when compared to single task (-0.462±0.097; -0.710,-0.214; t_{57}= 5.853, p<0.001) and dual task (-0.386±0.094; -0.62,-0.148; t_{57}=4.483, p=0.001). No significant difference was found between single and dual tasks for μ-value (p>0.9). The results of the ANOVA test also yielded significant effect of trial type; i.e. significantly larger μ-values were measured for return trials than target trials (0.534±0.095; 0.729, 0.340; f_{1,28}=31.764, p<0.001). There was no significant interaction between task and trial for μ-value. Figure 19 shows μ-values measured for different task and trial types. However, due to the low number of trials in our saccade experiment, we further tested our results in saccade experiment 2, as explained in the next section.
Figure 19: Rate of rise in saccade decision signal (µ-value) across task conditions and trial types. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p< 0.0001; **0.001<p< 0.01; *0.01<p<0.05.

3.1.2. **Saccade experiment 2**

As explained before, we were only interested in analyzing the latency of the saccades for target trials when using the LATER model distribution of saccade latency. To do that, we ran saccade experiment 2. The result of saccade experiment 2 for log-likelihood of shift versus swivel was similar to the results obtained in experiment 1 that used the same tasks, but smaller numbers of trials. As shown in Figure 20, our results obtained using the LATER model latency distribution agreed that a general shift was favored over a general swivel (ΣLLR = -10.973).
LLR = -10.631
\( \mu_1 = 5.41, \mu_2 = 5.5, \mu_3 = 4.9, \sigma = 0.67 \)

(a)

LLR = -2.011
\( \mu_1 = 5.1, \mu_2 = 5.17, \mu_3 = 4.34, \sigma = 1.1 \)

(b)

LLR = 1.845
\( \mu_1 = 5.68, \mu_2 = 6.18, \mu_3 = 6.00, \sigma = 0.75 \)

(c)

LLR = -0.425
\( \mu_1 = 5.66, \mu_2 = 5.78, \mu_3 = 5.62, \sigma = 1.09 \)

(d)
Figure 20: Distribution of prosaccade latencies using best fit for prosaccades towards randomly presented eccentric targets under single (red dots, $\mu_1$), dual (blue dots, $\mu_2$), and triple restricted (green dots, $\mu_3$) task conditions. All participants except (c) and (f) showed that shift was favoured over swivel (LLR<0). Using the Kolmogorov-Smirnov test, the values of $\sigma$ and $\mu$ were calculated for the fitted lines with a fixed slope.
3.2. Secondary saccades

Two-way ANOVAs for repeated measures tested any significant effect of task and trial type on latency, gain, and ratio of secondary saccades. The ratio of secondary saccades was calculated as the frequency of secondary saccades divided by the frequency of initial saccades for each participant, across tasks and trial types. The results did not show any significant effect of task or trial type on latency and gain of secondary saccades (p>0.05). Figure 21 (a-d) shows latency, gain, and ratio of secondary saccades.

The ratio of secondary saccades was significantly affected by trial type; i.e. target trials showed more secondary saccades than return trials (0.137 ± 0.20; 0.96, 0.179; f_{1,24}=46.439, p<0.001). The interaction between the task and trial type was significant for the occurrence of secondary saccades (f_{2, 48} = 5.768, p=0.006). Post-hoc paired t-tests compared the ratio of secondary saccades in the three tasks, separately for target trails and return trials. The results for target trials showed significantly more secondary saccades under the dual task in comparison with the triple task (0.123 ± 0.024; 0.061, 0.186; t_{29}=5.207, p<0.001). No significant main effect of task was found for the occurrence of secondary saccades in return trials (p>0.3).

3.1. Final saccadic end position

Final saccadic end position (total gain of consecutive saccades to get on the desired target position) was not influenced by task condition or trial type. The test of normality did not show a normal distribution for the final saccadic end position measured in the dual-task condition (for target trials: p<0.001, for return-trials: p<0.001). Thus, the analyses were done with nonparametric tests for related samples; and similar results were obtained. Figure 22 shows the percentage error in final saccadic end position across task conditions and trial types.
Figure 21: Latency (a), gain (b) and ratio of secondary saccades, defined as frequency of secondary saccades divided by frequency of initial saccades (c), across task conditions and trial types within subjects. Pair-wise comparisons were conducted using post-hoc analyses for repeated measures ANOVA.$^{***} p < 0.0001$. 
Figure 22: Percentage error in final saccadic end position across task conditions and trial types. Error bars indicate standard errors from the mean.

3.2. Target acquisition time

A two-way ANOVA for repeated measures tested any significant effect of task and trial type on target acquisition time. Trial type significantly affected target acquisition time; i.e. longer target acquisition time was measured for target trials compared to return trials (98.99 ± 10.569 ms; 77.145, 120.846; f_{1,23}=87.841, p<0.001). There was a significant interaction between trial type and task for target acquisition time (f_{2,46}=15.167, p<0.001). The results also showed that task condition significantly affected target acquisition time (f_{2,46}=33.356, p<0.001). For each target and return trial, post-hoc paired t-tests compared target acquisition time between the tasks (figure 23).

Target acquisition time was significantly longer for the triple task when compared to dual task (for target trials: 37.520± 9.634 ms; 12.725, 62.315; t_{26}=9.038, p=0.002.; for return trials: 32.74± 12.218 ms; 1.548, 63.919; t_{28}=3.405, p=0.037). Triple task showed significantly longer target acquisition time also when compared to the single task (for target trials: 116.886 ± 12.868
ms; 83.769, 150.002; t_{25}=4.170, p<0.001.; for return trials: 42.667±12.699 ms; 10.25, 75.08; t_{28}=2.679, p=0.007).

The dual task showed a longer target acquisition time than the single task only for target trials (79.366 ± 11.642 ms; 49.404, 109.327; t_{24}= 6.817, p<0.001).

Figure 23: Target acquisition time across task conditions and trial types. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p<0.0001; **0.001<p< 0.01; *0.01<p<0.05.
3.3. Correlation results for workload indicators

3.3.1. Acuity experiment

A significant correlation was found between heart rate and MTE score (Pearson correlation: \( r=0.270, p=0.012 \)). No significant correlation was found between task performance and physiological indicators of mental workload in the acuity experiment.

3.3.2. Saccade experiment

A significant correlation was found between heart rate and MTE score (Pearson correlation: \( r=0.263, p=0.021 \)). Higher heart rate was significantly correlated with latency of saccades (for target trials: \( r= 0.330, p= 0.003 \); for return trials: \( r= 0.220, p=0.048 \)). Participants with greater MTE scores showed longer target acquisition time (for target trials: \( r=0.601, p<0.001 \); for return trials: \( r=0.208,p=0.064 \)) and longer latency of saccades (at target trials: [mean latency: \( r=0.447,p<0.001 \); median latency: \( r=0.314,p=0.005 \)]; at return trials: [mean latency: \( r=0.349,p<0.001 \); median latency: \( r=0.282,p=0.012 \)].

Longer subjects’ reaction time was associated with smaller \( \mu \)-values (\( r= -0.279, p=0.034 \)) and longer target acquisition time (\( r = 0.313, p=0.015 \)). Participants with more manual response errors showed significantly greater workload measures (MTE score: \( r=0.695, p\text{-value}<0.001 \); heart rate: \( r=0.486, p<0.001 \); skin conductance level: \( r= 0.304, p=0.023 \)), less occurrence of secondary saccades (\( r=-0.401, p= 0.001 \)), and a trend towards greater error in final saccadic end position (\( r =0.238, p=0.072 \)). Fewer secondary saccades were also associated with greater MTE score (\( r= -0.318, p=0.004 \)) and the longer latency of saccades (\( r= -0.380, p<0.001 \)).

No other correlation was statistically significant.

4. Discussion

4.1. Physiological workload indicators

Mental states such as stress and cognitive load are mediated by the sympathetic system that is activated through excitation of the posterior hypothalamic nucleus and inhibition of the Edinger-
Westphal nuclei, which also serves to decrease (relax) activity of the parasympathetic system (Granholm & Steinhauer, 2004; Steinhauer et al., 2004). Mental effort induced by arithmetic tasks, such as serial subtraction, is one of the most common stressors used in the laboratory to index cardiovascular changes (Zygmunt & Stanczyk, 2010). Mental arithmetic can produce substantial cardiovascular, adrenocorticotropic hormone, and cortisol responses (Allen, Obrist, Sherwood & Growell, 1987; Grossman & Svebak, 1987; Hjemdahl et al., 1989; Sloan, Korten & Myers, 1991; Al'Absi et al., 1997; Kamiya, Iwase, Michikami, Fu & Mano, 2000; Freeman, 2006; Liu, Iwanaga & Koda, 2011). Mental arithmetic is a simple method to induce mental and psychological stress, which can elicit sympathoadrenal discharge, and is found to be similar to psychological stressors, such as playing video games, in its ability to decrease inhibition of parasympathetic activity (Turner & Carroll, 1985). The changes in autonomic nervous system activity due to mental arithmetic can be indexed in various physiological measurements. Those used in the current study include heart rate, skin conductance level, and pupil size. Below, the effects of mental workload on each of the physiological measurements of mental workload used in our study have been discussed.

### 4.1.1. Heart rate

The increase in heart rate has been frequently documented in the presence of doing an arithmetic task (Sloan et al., 1991; Willemsen, Ring, McKeever & Carroll, 2000; Tanida, Sakatani, Takano & Tagai, 2004; Freeman, 2006; Liu et al., 2011). Our results showed that heart rate increased significantly when performing the arithmetic task; whilst performing the visual discrimination task by itself did not reveal a significant change in heart rate. These findings agreed with an increase in sympathetic and a decrease in parasympathetic activity of the autonomic nervous system that was indicated via changes in heart rate during challenging tasks such as arithmetic (Berntson et al., 1994).

Investigation of cardiovascular measurements at different difficulty levels of memory tasks showed that energy consumption of the heart due to challenging tasks is mediated by the beta-adrenergic pathway (Richter, Friedrich & Gendolla, 2008). Tasks such as mental arithmetic, which evoke active coping behavior, act to produce a shift in baseline heart rate between subjects. Consequently, greater baroreflex inhibitory control of sympathetic activity and more parasympathetic response to stressors may be recorded in females (Willemsen et al., 2000), as
female are known to have lower sympathetic tone than males (Dart, Du & Kingwell, 2002; Hogarth, Mackintosh & Mary, 2007). However, we found no significant difference between gender groups in terms of physiological changes due to the task. This finding is in agreement with Linden (1991), who suggested that gender differences may be dampened when task complexity increases. Therefore, we concluded that our tasks with arithmetic were challenging enough for both gender groups to induce stress.

Willemsen et al. (2000) compared cardiovascular activity at various task intervals across different difficulty levels of mental arithmetic, each lasting for 8 min. The results showed no significant difference in the elevated heart rate across various difficulty levels of mental arithmetic. Although heart rate (HR) increased less during the first minute of doing arithmetic tasks, cardiovascular activity remained elevated throughout the whole task. Additionally, when separate resting measurements were done for each task, no significant difference was found across task conditions. The results obtained by Willemsen et al. (2000) support the idea that the increase in HR found in our experiments was not due to the time required to complete a task, or due to using a similar resting level for both acuity and saccade experiments. Instead, our results could be due to a higher level of mental load induced by the triple restricted saccade task and restricted acuity task conditions.

Although some previous studies showed that HR is unaffected by manipulation of task difficulty (Linden, 1991; Carroll et al., 1996; Willemsen et al., 2000), a greater increase in HR from resting level can be measured with task novelty due to beta-adrenergic activation of the autonomic cardiovascular system (Willemsen et al., 2000; Sosnowski, Krzywosz-Rynkiewicz & Roguska, 2004). This may account for the significant increase in our HR measurements for the baseline task (calibration run) compared to the resting level among our normal participants. The calibration run was the first task that all participants were required to do in the lab, and our normal participants were naïve to wearing the eye tracker and eye movement recordings. However, this was not the case for our participants with nystagmus, all of whom had participated in eye movement recordings in a similar lab setting before. This could explain why the calibration task was not stressful enough to change HR significantly in the nystagmus group (as reported in a later chapter), but increased from resting level in our naïve normal group as they experienced eye movement recordings for the first time at the calibration run.
Our finding of no marked change in subjects’ manual response times with the arithmetic task agreed with previous studies indicating that heart rate is more sensitive to an arithmetic task than subjects’ reaction time (Allen et al., 1987; Allen & Crowell, 1989; Sosnowski, Bala & Rynkiewicz, 2010). Two controlling mechanisms have been suggested for mental tasks: the first one is the beta-adrenergic (sympathetic) system, which supports energy consumption and is mostly involved in reaction time tasks; and the other system is related to the supervisory cognitive control of intended behavior during problem solving tasks, which is mediated by parasympathetic withdrawal (Campbell, 1960; Allen & Crowell, 1989; Jennings & van der Molen, 2002; Sosnowski et al., 2010). Cardiovascular measurements have shown sympathetic activity increases for the task during which effort is allocated to perform arithmetic problems (Sosnowski et al., 2010). Consistent results have been obtained using event-related potential waveforms (Liu et al., 2011). The event-related potential waveform (P300) reflects the endogenous potentials and cognitive process in the brain and can be recorded by electroencephalography (Chapman & Bragdon, 1964). The amplitude of P300 reflects the amount of available cognitive resources allocated for stimulus evaluation (Kaseda, Jiang, Kurokawa, Mimori & Nakamura, 1998). The latency of P300 reflects the time required to evaluate stimuli (Salisbury, Desantis, Shenton & McCarley, 2002). Liu et al. (2011) recorded P300, level of wakefulness, and HR for a 28 min arithmetic task. The results showed higher levels of wakefulness, an increase in HR, and larger amplitude but no change in the latency of P300 due to arithmetic tasks, which indicated more cognitive resources were required to maintain task performance during active stress exposures such as arithmetic. This suggested a greater oxygen supply to the brain during the arithmetic task is required to maintain task performance (Liu et al., 2011).

Overall, our results for restricted tasks are consistent with the notion of more brain oxygen supply and energy consumption with the increased capacity of cognitive resources allocated to cover task demands (Sosnowski et al., 2010; Liu et al., 2011) that were required for a higher level of mental effort (Eggemeier, 1988). Hence, our results for heart rate agreed that a high level of mental workload was induced during our restricted tasks in both acuity and saccade experiments.
4.1.2. **Pupil**

As explained above, mental arithmetic can demand an active coping behavior and therefore would appear to be an effective, active, and consistent type of mental stressor, and results both in sympathetic outflow and a decrease in parasympathetic inhibition (Allen et al., 1987; Grossman & Svebak, 1987; Hjemdahl et al., 1989; Sloan et al., 1991; Al'Absi et al., 1997; Kamiya et al., 2000; Freeman, 2006; Liu et al., 2011). Pupil dilation is driven by the sympathetic pathway and supported through the inhibition of parasympathetic components (Granholm & Steinhauser, 2004; Steinhauser et al., 2004). Pupil dilation is strongly associated with activity of the locus coeruleus (Aston-Jones & Cohen, 2005; Sterpenich et al., 2006). The locus coeruleus is a part of the brain stem that has a main role in the release of noradrenaline (Foote & Morrison, 1987). The complex of locus coeruleus--noradrenaline has been found to facilitate task engagement, attention, perceptual acuity, and decision processes (Bouret & Sara, 2005; Sara, 2009). Both direct cortical and indirect cortico-thalamic-hypothalamic pathways heavily contribute to the inhibition of the parasympathetic pathway to the Edinger–Westphal nucleus to dilate pupils (Lowenstein, 1955).

Davis, Daluwatte, Colona and Yao (2013) investigated the physiological effects of mental arithmetic on pupil size by measuring time and amplitude of the pupillary light reflex before, during, and after mental arithmetic. The results showed both constriction and re-dilation times increased when sympathetic activation increased to dilate the pupil, suggesting a level of parasympathetic activity at the pupillary sphincter during the early stage of re-dilation (Davis et al., 2013).

Previous studies have reported that pupil size increased 0.5±0.2 mm (mean± SD) under various types of cognitive tasks, while counting tasks could dilate the pupil ≥ 0.16 mm (Hess & Polt, 1964; Granholm et al., 1996). Visual tasks and target detection can affect pupil size (Privitera, Renninger, Carney, Klein & Aguilar, 2010). Visual demand, attention, stress, increased task difficulty, cognitive load, and mental activity have been known to cause pupil dilation (Hess & Polt, 1964; Beatty, 1982; Granholm et al., 1996; O'Neill & Zimmermann, 2000; Steinhauser, Condray & Kasparek, 2000; Recarte & Nunes, 2003; Iqbal, Zheng & Bailey, 2004; Steinhauser et al., 2004; Porter, Troscianko & Gilchrist, 2007; Wierda, van Rijn, Taatgen & Martens, 2012). Our finding for an increase in pupil size during a discrimination task is similar to the results obtained in the previous studies, which indicated that the pupils dilate in visual detection or discrimination tasks (Hahnemann & Beatty, 1967; Privitera et al., 2010). This could
be due to a higher level of visual demand, task engagement, and attention being required to perform the discrimination tasks (Hoeks & Levelt, 1993; Karatekin, Couperus & Marcus, 2004; Einhäuser, Stout, Koch & Carter, 2008).

Larger pupillary responses have been reported for tasks during which participants were required to press a button, indicating a greater engagement level in the task when manual responses were required (Einhäuser et al., 2008; Privitera et al., 2010). Privitera et al. (2010) found that pupil dilation at a visual detection task with no response required was less than in the task in which a button response was required, even if the response was missed. Target detection resulted in a small and early pupil constriction that was immediately overcome by stronger pupil dilatory movements (Privitera et al., 2010). Larger pupil dilation was also recorded under uncertainty of subjects’ responses (O’Neill & Zimmermann, 2000). Less pupil dilation has been recorded for missed responses, suggesting that pupil dilation is affected by, but not dependent on, the subjects’ report seeing targets (Privitera et al., 2010). The tight relationship between the locus coeruleus-noradrenaline complex and pupil size has been suggested previously to explain pupil dilation at visual detection tasks, even in the presence of uncertainty or missed responses (Aston-Jones & Cohen, 2005; Sterpenich et al., 2006; Privitera et al., 2010). Hence, we can conclude that the larger pupil size measured during the discrimination task in our experiments may index a higher level of the decision-making process and subjects’ involvement in the tasks even in the presence of missed or uncertain responses (O’Neill & Zimmermann, 2000; Privitera et al., 2010).

Increase in pupil size has been found previously in accordance with the difficulty level of an arithmetic task (Hess & Polt, 1964). We also found that the pupils dilated as a function of task difficulty and level of mental load. This finding agreed with previous studies which have shown that the pupil responds sensitively to higher levels of task demands, increased difficulty level, and the amount of processing load (Granholm et al., 1996; O'Neill & Zimmermann, 2000; Just, Carpenter & Miyake, 2003; Recarte & Nunes, 2003; Steinhauser et al., 2004). However, this phenomenon only occurs within the threshold of processing capacity (Just et al., 2003). Pupil dilation has been suggested to differentiate task difficulty levels (Steinhauer et al., 2004). The amount of dilation for concurrent tasks is less than the sum of the dilation measured for each task alone. This suggests that pupil dilation reflects total brain activation (Just et al., 2001) and is
affected by the capacity of information processing resources used to cover task demands (Just et al., 2003; Verney, Granholm & Marshall, 2004).

It has been suggested that cognitive tasks including counting, talking and visual detection share common attentional resources (Recarte, Pérez, Conchillo & Nunes, 2008). The systematic increase in pupil size across our tasks is in line with more information processing and allocated capacity of resources (Beatty, 1982; Granholm et al., 1996; O'Neill & Zimmermann, 2000; Steinhauer et al., 2000; Just et al., 2003; Recarte & Nunes, 2003; Steinhauer et al., 2004). Our findings also parallel previous findings of pupillary dilation during sustained cognitive load (Steinhauer et al., 2000; Steinhauer et al., 2004). Measuring pupil dilation under different pharmacological conditions to control the autonomic nervous system has shown that sustained performance in difficult tasks is modulated by cortical inhibition of the parasympathetic system rather than the sympathetic pathway. Reticular pathways contributing to arousal and fronto-cortical functions in demanding cognitive tasks have been suggested to dilate pupils through parasympathetic inhibition mediated by the Edinger–Westphal nucleus (Steinhauer et al., 2004).

We found pupil dilation for the acuity experiment was not influenced by gaze position, possibly due to the small elliptical effect and optimal baseline level measured for each gaze position. However, we noticed that pupil size tended to be larger at primary gaze position under unrestricted conditions, possibly because our acuity experiment always started by presenting the unrestricted task at central gaze. This may reflect the primary effect of the task requiring greater attentional resources at the start of the experiment, which would occur when presenting central stimuli compared to those at the other positions. This possibility agrees with the idea that preparatory pupil dilation reflects dorsolateral prefrontal activity due to the immediate demands imposed by the new task instruction, while less pupil dilation could be due to the brain activity during sustained processing (MacDonald, Cohen, Stenger & Carter, 2000; Siegle, Steinhauer, Stenger, et al., 2003; Siegle, Steinhauer & Thase, 2004). Whilst both sympathetic activation and parasympathetic inhibition contribute to pupil dilation during sustained attention, greater pupil dilation in response to a higher level of task demand is largely associated with cortical parasympathetic inhibition (Steinhauer et al., 2004). Both direct frontal functioning and indirect cortico-thalamic-hypothalamic pathways can inhibit the Edinger-Westphal nucleus for the purpose of parasympathetic inhibitory pupil dilation (Lowenstein, 1955). The elliptical effect on pupil measurements can be more noticeable as the eccentricity of gaze position increases (Gagl,
Hawelka & Hutzler, 2011; Brisson et al., 2013). Moreover, the subsequent eye movements required during the saccade experiment might result in various mental load levels and hence pupil sizes across gaze positions. Although pupil dilation varied with gaze position, the possible effect on our pupil data does not interfere with our main research question regarding increased level of subjects’ mental load with increasing task difficulty. Our results showed that the pupil dilated from baseline across all gaze positions, and thus agreed with the idea that subjects’ sustained attention and effort systematically increase with task demands for each gaze position (Beatty, 1982;Granholm et al., 1996; O’Neill & Zimmermann, 2000; Steinhauer et al., 2000; Just et al., 2003; Recarte & Nunes, 2003; Steinhauer et al., 2004).

Factors other than mental load, such as preparation for the next saccade and for manual responses, might influence pupil dilation. According to previous studies (Hupe, Lamirel & Lorenceau, 2009;Jainta, Vernet, Yang & Kapoula, 2011), the pupil also dilates in the presence of manual responses and when preparing for saccade execution (700 and 300 msec preceding the response, respectively). However, less pupil dilation has been measured with longer saccade latencies (Jainta et al., 2011). Response uncertainty resulted in less pupil dilation during a four choice response selection task, whilst a larger pupil size could be measured in advanced response selections (Moresi et al., 2008). We measured an increase in pupil dilation and subjects’ response errors with mental arithmetic for both acuity and saccade experiments. Knowing this, our results suggested pupil size was more influenced by the level of visual attention and processing load rather than by task manipulations for each experiment, such as preparation of saccades or manual responses.

4.1.3. Skin conductance level

For both acuity and saccade experiments, skin conductance level (SCL) significantly increased during the tasks with mental arithmetic and time restriction relative to other tasks. As we explained in the previous chapter, SCL can show the corresponding changes in the level of task involvement in information processing (Vernet-Maury et al., 1995; Nourbakhsh et al., 2012; Salvia et al., 2013). Skin conductance has been shown to reflect the general excitation level and the total level of task demands during both information intake and cognitive processing (Tursky et al., 1970). The magnitude of the change in SCL is related to the difficulty of the problem solving task with respect to energy mobilisation, and more precisely “effortful allocation of
attentional resources” to cover task demands. In other words, the change in SCL indicates the level of task engagement and active problem solving (Pecchinenda (1996); Critchley et al. (2000). Thus, increased SCL measured for the tasks with mental arithmetic could have been caused by a stronger sympathetic response for energy mobilization as indicated by increased heart rate; i.e. the effort exerted by the participants to cover task demands.

Johnson (1966) measured HR and SCL at three levels of task difficulty for visual tasks and verbalisation tasks during which participants were required to verbally describe stimuli. The results showed both HR and SCL increased during verbal activity. According to Johnson (1966), level of visual attention alone cannot induce enough excitation to change SCL or HR; however, a corresponding trend can be seen with increasing complexity of the task. Similarly, we found SCL tended to increase as task difficulty increased; however, no significant change was found for SCL due to the discrimination task alone in the acuity experiment. The possible reasons for this finding are discussed below.

It has been stated that skin conductance does not respond well to attentional level, but can differentiate between overt and covert responses. Conversely, heart rate is more sensitive to the level of attentional demand, but less to the type of response (Tursky et al., 1970). While both of our tasks with mental arithmetic required both verbalisation and button pressing, eye movements were also required as an overt response in the saccade experiment. Possibly, the eye movements required for the saccade experiment enhanced SCL; thus, SCL was significantly increased during the unrestricted dual task as compared to the single task. A larger increase in mean heart rate from resting level in the triple saccade task (10 bpm), compared with the restricted acuity task (6 bpm), also indicates that energy mobilisation differed between these tasks.

Another possible reason for this finding is that skin conductance level increases more under psychological stresses such as fear, rather than under cognitive loads such as mental arithmetic (Setz et al., 2010). All participants were required to do the saccade experiment before the acuity experiment; thus, they might have been expected to experience more stress psychologically for the saccade task rather than for the acuity tasks. Moreover, they seemed to be less interested in performing the second experiment that involved the condition with and without arithmetic (usually reacting in a negative way e.g., saying ‘oh no!’); knowing this, the lower level of subjects’ engagement in the acuity experiment might contribute to the fewer sympathetic effects of task demands, as explained previously (Willemsen et al., 2000).
Thus, the significant changes in both HR and SCL found in our experiments with arithmetic could be due to factors beyond acuity demand and verbal or manual responses. Instead, the changes in HR and SCL might have been induced by an increase in overall cognitive load and mental stress.

Overall, the physiological measurements i.e., pupil size, HR, and SCL are in accordance with high level of mental workload was induced by the tasks with mental arithmetic and time restriction. However, there was a lack of comparability across the measurements. Both HR and SCL did not show significant changes due only to the secondary task; i.e., visual discrimination. However, the subjective test and pupil dilation could sensitively differentiate between task difficulty levels. In contrast with SCL, which significantly varied only across saccade tasks, heart rate responded sensitively to mental stress and increased only with arithmetic in both experiments. Our results agreed with the idea that a higher level of workload shown in one physiological measure did not necessarily lead to significant changes in other measures. This discrepancy can be explained in terms of sensitivity of one test over the other in terms of different task contexts (Wickens, 2002; Ryu & Myung, 2005).

4.2. Task performance

We did not find any significant change in contrast level reached across gaze positions and task conditions in normal participants, but the smallest optotype size achieved increased under high mental load (i.e., the larger final target size indicates that performance worsened). In contrast to individuals with nystagmus, in whom vision is usually markedly affected by gaze position, a constant visual threshold would be expected in normal participants, irrespective of gaze position (Hertle et al., 2002; Yang et al., 2005). An earlier study found that visual threshold in participants with normal ocular health is not influenced by the difficulty levels of the task (Bohdanecky, Indra & Radil, 1989). Unlike participants with nystagmus, forced time-restriction did not change visual acuity in normal controls (Yang et al., 2005). It is worth noting that our experimental set-up was limited to the range of acuity targets that could be presented, due to the resolution of the display projector. To ensure that recognition difficulty could be maintained even for the normal participants, the contrast of the acuity targets was also reduced. We did not aim to measure visual acuity as the minimum angle of resolution, although this could have been
of interest had it been technically feasible. Instead, we aimed to increase the difficulty level of the visual targets by reducing both their size and their contrast.

Although the attention and effort needed to respond to task demands usually increases with task difficulty, the level of task engagement and active coping should be assessed using the physiological measurements which, in contrast to subjective scales, are less biased by emotional factors (Pecchinenda, 1996). There is also an interaction between subjective mood and task difficulty which can change the level of effort expended (Gendolla & Krüsken, 2001). Contrary to emotions, subjects’ moods can be experienced without simultaneous awareness of their cause (Keltner & Gross, 1999). In active coping, positive or negative moods are defined based on the subjects’ confidence in their own abilities to cover the task demands. A subject with a positive mood and optimistic feelings will have higher confidence in their ability to cover task demands, a subject with a negative mood and pessimistic feelings will have lower confidence in their ability to cover task demands. A low level of task difficulty combined with a negative mood may increase the effort and thus the related physiological responses. A low difficulty level can result in a decrease in physiological responses if the level of subjective demand to give effort is also low rather than high; in other words, if the subject has a positive mood rather than a negative mood, they will put less effort in their task. It is the opposite for highly difficult tasks. In a difficult task, stronger physiological responses can be recorded with a positive rather than a negative mood, since subjects’ positive feelings can result in more active coping and task engagement; in other words, the level of subjective demand is high, but not yet too high that the subjects cannot cope (Gendolla & Krüsken, 2001). Although we did not measure subjects’ mood, the physiological measurements are in accordance with the subjects’ rating scale; this agrees with the ideas that the level of effort expenditure increased for the tasks with mental arithmetic, and our participants actively coped with the task demands.

The efficiency of information processing can be reflected in subjects’ task performance in terms of both speed and accuracy of the responses (Flehmig et al., 2010; Salvia et al., 2013). All of our participants were required to be actively involved in the arithmetic task while giving verbal responses within 5 sec. We did not record our subjects’ task performance for the arithmetic task as it aimed to be a disruptive task to induce mental load while doing the discrimination tasks. The characteristics of approach or avoidance of doing discrimination tasks with mental arithmetic could lead to two behavioral profiles to deal with the discrimination tasks.
The first focuses on the accuracy of response at the expense of speed, and the second is to respond faster without being concerned about the accuracy (Flehmig et al., 2010; Salvia et al., 2013). The possibility of a trade-off between speed and accuracy for the manual responses can be increased when the number of inaccurate responses increases during the tasks with both time restriction and arithmetic. However, we found task performance degraded more due to missing responses rather than incorrect submitted responses. More manual responses might have been recorded for the tasks with arithmetic if participants had a longer time to respond. It looked as if participants were concerned about the accuracy of responses at the expense of time. That is in agreement with the trade-off between speed and accuracy of task performance.

Recarte and Nunes (2003) described three steps for visual tasks including target detection, target identification, and subjects’ response to the target, when investigating decision-making problems in the presence of mental load (detected by pupil dilation during a simulated driving task with talking on a phone as a secondary task). The results showed that mental load can limit processing capacities, resulting in later target detection, poorer target discrimination, and to a lesser degree, inappropriate response time (Recarte & Nunes, 2003). We did not find any significant change in either manual response time (RT) or visual processing time across task conditions. Similar to Recarte and Nunes (2003), we recorded more response errors during the tasks with arithmetic due to poor task performance rather than time restriction. We agree with Recarte and Nunes (2003), who suggested that attention allocation to internal distractions influences the capacity of visual processing and limits application of top-down processes. Although participants were asked before, and frequently during, the task to not miss any manual responses, a higher number of lapsed responses were recorded for the discrimination task in the triple task. In spite of similar acuity demand and final saccadic end position across tasks, task performance deteriorated for the triple task as compared with the dual task. That indicates our participants engaged less with manually responding to visual targets, whilst concurrently performing arithmetic problems. Since visual processing time did not differ across our task conditions, degraded performance in the manual task with mental load was not due to late target recognition, but could be associated with degraded information processing under this mental load. Hence, we believe degraded information processing due to the limited capacity of available resources rather than a shortage of processing time resulted in degraded task performance with the higher mental load.
Overall, the results of the experiments in the normal participants indicated the experimental procedures could have contributed to a higher workload and induced mental effort when performing the tasks with arithmetic. Hence, the experiments could also be run using the same protocol to investigate the effects of the workload in the participants with nystagmus. Due to the same equipment limitation explained before, the range of logMAR target sizes that could be presented in the acuity experiment is above the binocular logMAR visual acuities of most patients with idiopathic INS, as described by Abadi and Bjerre (2002), and we could not measure the actual threshold visual acuity. The details of the experiments performed in nystagmus group will be explained in the next chapter.

In the following sections, we will discuss how the results of the saccade task could be affected by task conditions, such that delayed saccade latency and target acquisition time could signify increased load in information processing, and the possibility of a distracted mind.

4.3. Eye movements

4.3.1. Peak velocity and saccade duration

While the centrifugal saccade usually moves the eyes towards a target of interest, the centripetal saccade has been described as returning the eyes to the primary orbital position (Pelisson & Prablanc, 1988). Marked asymmetries between velocity and duration of saccades have been found depending on whether the initial saccade position was either centrifugal or centripetal (Collewijn, Erkelens & Steinman, 1988; Pelisson & Prablanc, 1988; Evdokimidis, Liakopoulos & Papageorgiou, 1991). We measured faster initial saccades for return trials than target trials. These findings are in agreement with the fact that centripetal saccades have higher velocity and shorter duration than centrifugal saccades (Täumer, Lemb & Namislo, 1976; Jürgens, Becker & Kornhuber, 1981; Collewijn et al., 1988; Pelisson & Prablanc, 1988; Becker & Jürgens, 1990; Rottach, Das, Wohlgemuth, Zivotofsky & Leigh, 1998).

It has been found that centripetal saccades have faster peak velocity and less skew (the duration of the accelerating phase of saccade divided by the total saccade duration) of the saccade profile than centrifugal saccades (Van Opstal & Van Gisbergen, 1987; Collewijn et al., 1988; Pelisson & Prablanc, 1988; Evdokimidis et al., 1991; Chen, Lin, Chen, Tsai & Shee,
The difference between centripetal and centrifugal saccades has been attributed to the high tension state of the antagonist muscle at eccentric gaze position prior to the centripetal saccades, in contrast to its initially low tension state preceding centrifugal saccades (Collewijn et al., 1988). Pelisson and Prablanc (1988) explained that the difference in centripetal and centrifugal saccades resulted from either mechanical differences in the push-pull arrangement of the peripheral oculomotor system, nonlinearity of neural command signals, or a combination of the two. In another study, Jürgens et al. (1981) suggested that differences in velocity and duration between saccade directions originate from saccadic innervations and the local feedback loop. However, the results of a later study by Koene and Erkelens (2002) found that the difference in the kinetics of centripetal and centrifugal saccades is not due to muscle innervation or neural feedback signals occurring during those saccades. These findings showed the main reason for the differences in kinetics between centripetal and centrifugal saccades to be the nonlinear force-velocity relationship of the eye muscles. They suggested greater viscous force was exerted during centrifugal saccades, thus slowing down the saccades, and resulting in lower peak velocity compared to centripetal saccades (Koene & Erkelens, 2002).

The differences between centripetal and centrifugal saccades were also studied in terms of the subjects’ efforts by using potential changes in cortical pre-motor negativity (PMN) preceding self-paced saccades. Earlier onset times and greater amplitudes were recorded for PMN prior to the onset of centrifugal than for centripetal saccades, suggesting that less effort is required for centripetal saccades (Koene & Erkelens, 2002). The higher effort required for centrifugal saccades has been explained in terms of the level of interest in the target and the extent to which it is visually demanding (Koene & Erkelens, 2002). Evdokimidis, Mergner and Lücking (1992) measured the PMN preceding visually guided saccades and refixation saccades during which the eyes returned to a predictable fixation point, usually less consciously and more reflexively. The results showed less PMN for centripetal refixation saccades than for the eccentric visually guided saccades. Centripetal refixation saccades showed a greater decline in PMN than eccentric refixation saccades that were directed towards an anticipated gaze position. The results obtained by Evdokimidis et al. (1992) agreed that less volitional effort is required to engage with centripetal saccades. In a previous study, Thickbroom and Mastaglia (1985) recorded a smaller amplitude of PMN and a greater slope and shorter duration of PMP (pre-motor positivity potential) for saccades that were time-predictable, compared to the saccades that were
unpredictable in terms of target onset. Since PMN refers to task preparation rather than physical movement alone, the results of previous studies (Thickbroom & Mastaglia, 1985; Evdokimidis et al., 1992) have indicated the elaboration of motor-related activity of the parietal visuomotor centers in relation to arousal level and preparation of the saccade. In our study, centrifugal saccades were elicited during target trials that were unpredictable in terms of both timing and location of the target onset. In contrast, each subjects’ manual response was followed by a return trial that could elicit a predictable saccade in terms of both timing and position of target onset. According to our results, saccadic peak velocity was not affected by task, nor did it change for different types of saccades. Hence, the variation in velocity of saccades was not due to the postsaccadic task demands, which were either fixation of a central point or the discrimination of a peripheral target. Our findings of higher peak velocities for initial saccades in return trials are consistent with the lower amount of volitional effort required for centripetal compared to centrifugal saccades, both in terms of less motor activity required and the predictability of the task.

However, studies using complex visual tasks such as driving or searching for an object, in which different levels of visual demand arise, showed that saccadic peak velocity can be increased as a result of higher task difficulty and cognitive demand (Di Stasi et al., 2009; Di Stasi, Renner, et al., 2010; Di Stasi, Antolí, et al., 2011; Di Stasi et al., 2012). Similar to our experiment, App and Debus (1998) analysed both target and return trials and showed a significant increase in saccadic peak velocity as the urgency and difficulty level of the visual task increased.

One possibility for finding no significant effect of the task conditions on asymptotic peak velocity of saccades in our study might be the task context, which involved no major change in the level of visual acuity demand across various conditions. Moreover, no feedback was provided on task performance. While the level of mental load changed for the triple task with the introduction of an arithmetic task, the complexity of the task in terms of visual demand remained unchanged. The visual target used in our experiment was large enough for the subjects to see and did not demand high acuity; this resulted in our subjects expending little effort to see the targets during the tasks, even under mental load. The use of time limits for manual responses also may not have been restrictive enough, as there were not any significant changes in manual response time or processing time due to task differences. As explained in the previous section, that more
response errors were recorded for the triple task agreed with a lack of visual attention and less engagement with the discrimination task while simultaneously doing arithmetic.

4.3.2. **Saccade latency**

Comparison of the latency of saccades across tasks and within subjects can be a non-invasive method to investigate the neural mechanism underlying decision making (Shadlen & Gold, 2004; Gold & Shadlen, 2007; Halliday & Carpenter, 2010). For each individual subject, the changes in saccade latency can inform us on how decision making processes can be affected by various factors, including external circumstances (Halliday & Carpenter, 2010). Prosaccades are not generated purely involuntarily and can be executed in a controlled way to improve the task performance; this is termed *controlled execution of saccades* (Stuyven et al., 2000). Higher cortical areas, including frontal or supplementary eye fields in the brain, contribute to the controlled execution of saccades that show longer latency than reflexive saccades. Moreover, the superior colliculus, which controls automatic reflexive saccades, is also controlled by higher cortical areas including frontal and dorsolateral prefrontal cortex (Johnston & Everling, 2008).

Results from the current study agreed with earlier work that the latency of initial saccades was affected by cognitive manipulations of the tasks, as shown by the finding that saccade latency increased significantly under the task with mental arithmetic and time restriction. Longer saccade latency in the presence of a high level of mental workload found in this thesis agrees with the results of previous studies showing the latency of prosaccades increased when saccades were executed under high levels of mental load and under decision making conditions (Roberts et al., 1994; Irving, Tajik-Parvinchi, Lillakas, González & Steinbach, 2009). Our finding of longer latency during the triple task is consistent with the controlled execution of saccades suggested by Stuyven et al. (2000) and supported the idea that prosaccade latencies can increase due to interference of a secondary cognitive task (Stuyven et al., 2000; Drewes & VanRullen, 2010, 2011).

However, our results did not show a significant change in saccadic latency when our participants were required only to perform a discrimination task at the post-saccadic position. In contrast with pointing movements to a visual target, saccadic eye movements can be initiated without a delay induced by interference of button pressing (Bekkering, Adam, Kingma, Huson &
Key pressing by finger tapping as a secondary task has been reported to induce no task specific interference effect on latency of saccades (Bekkering et al., 1994). One possibility for our results showing no significant effect of the dual task on saccade latency could be due to the ease of the secondary task used; the secondary task consisted of manually pressing the right or left key of a game controller to identify the direction of the E target. This possibility is consistent with the results obtained by Stuyven et al. (2000) indicating that the significant difference in saccadic latency was not due solely to finger tapping, but was instead found to be correlated with the level of cognitive load accompanying the manual task. In another study, no dependency or systematic interaction was found between rhythmic finger tapping and prosaccade latency, suggesting no competition of the shared neural processing resources when the cognitive load of the tapping task was too small (Sharikadze, Cong, Staude, Deubel & Wolf, 2009). According to previous studies (Bekkering et al., 1994; Stuyven et al., 2000; Sharikadze et al., 2009), the increased saccadic latency found in our study could be a result of the cognitive load induced by mental arithmetic and does not seem to be induced by motor interference stemming from a required manual response.

The results obtained from fMRI during combined saccade and visual detection tasks showed that attentional processing and oculomotor processing are integrated tightly at the level of the parietal, frontal, and temporal lobes (Corbetta et al., 1998; Simon et al., 2002). Attention and saccade tasks result in activation of the dorsal parietal lobe bilaterally (Simon et al., 2002). Both attention and saccade tasks can activate the frontal eye fields bilaterally as well as the supplementary eye fields (Simon et al., 2002). Programming a saccade toward a selected target seems to be closely coupled with visual programming for detection or recognition tasks at a neural level (Hoffman & Subramaniam, 1995; Kowler, Anderson, Dosher & Blaser, 1995). An increase in latency of saccades has been reported for times during which participants were required to respond to a target presented at a different position from the position of the desired target (Deubel & Schneider, 1996). Performance could be optimal when the target used for the saccade task and the recognition or discrimination task overlapped. The task demands and visual processing to discriminate a saccade target facilitate the saccade task performance by increasing a shift of attention to the same target position rather than evoking competition between saccade and discrimination tasks (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005; Van Stockum et al., 2011). The combination of a discrimination task with a saccade task allows investigation of
the extent to which bottom-up visual inputs and top-down controlling system, in the absence of a competition between them, affect the saccades. Hence, saccade execution is facilitated when it is concurrent with a discrimination task performed on the same target (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005; Van Stockum et al., 2011); however, the production of express saccades can remain relatively unchanged (Van Stockum et al., 2011). This is similar to how we presented Tumbling-E letters in our dual and triple tasks. Since the target used for the discrimination task was co-located with the target position used for the saccade task, it seems that the level of attention to the visual targets in our dual task could have increased or remained relatively close to the condition used in our single task condition. Similar to the results obtained by Van Stockum et al. (2011), we did not find any significant change in production of express saccades in the presence of a concurrent discrimination task.

Some previous studies have shown that latency of prosaccades decreased when the position of the saccade target overlapped with the position of the target used for an identification task (Guyader et al., 2010) or a discrimination task (Montagnini & Chelazzi, 2005). However, neither type of saccades, nor the latency of the saccades in our experiment, differed between the single and dual task condition. This discrepancy between our results and such studies mentioned above can be explained in terms of urgency level. Montagnini and Chelazzi (2005) have explained the reduction in saccade latency as being due to perceptual urgency of saccade execution, that is; when eliciting a saccade is essential to perform the other task. However, task instructions and cognitive demand can also influence saccade latency. In other words, the amplitude of effects of task demands on saccade latency can be dependent on the resources shared with saccades (Guyader et al., 2010). In the case of an identification task added to a saccade task, neural resources at the prefrontal and frontal cortex shared with saccades can affect the latency of a saccade (Guyader et al., 2010). When a saccade is required to respond to a target, perceptual urgency is increased and saccade execution prevails over the other task demands. This results in a level of motivation to generate an eye movement towards the target of interest that can involve the anterior cingulate cortex (Montagnini & Chelazzi, 2005; Guyader et al., 2010). Anterior cingulate cortex (ACC) is a brain region that is linked with internal states such as attention, cognitive processes, and affective behavior (Cardinal, Parkinson, Hall & Everitt; Davis et al., 2005). It has been known that the posterior part of the ACC contributes to the execution of eye movements by the projections to the brain stem, directly or via early activation of the ocular
motor areas in frontal cortex (Gaymard et al., 1998). Unlike some previous studies where saccade latency decreased when a post-saccadic task was added (Montagnini & Chelazzi, 2005; Guyader et al., 2010), saccade latency only tended to decrease with our discrimination task. A decrement in saccade latency in the presence of a post-saccade task is consistent with perceptual urgency of a saccade; this refers to an enhancement in generation of a saccade which is needed to perform another task (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005; Guyader et al., 2010; Van Stockum et al., 2011). However, the amount of the enhancement in saccade execution due to our discrimination task was not large enough to cause a significant change in saccade latency (i.e., there was no significant change in saccade latency when introducing only a discrimination task). It is also worth noting that no time restriction was used for presentation of the discrimination target in our dual task condition. Moreover, the discrimination task itself did not require a high level of visual acuity. The ease of the discrimination task and unlimited time available could have resulted in a lower level of perceptual urgency of saccades and can explain the lack of comparability between our dual task and single task for latency of saccades.

As explained above, a source of the significantly longer saccade latency recorded during the triple task in comparison with the single and dual tasks could be the task demands, as they have the potential to either enhance saccades or interfere with saccade execution (Guyader et al., 2010). Prosaccades are susceptible to attentional disruption when they need to compete with attention to allocate the required capacity of information processing (Pashler, Carrier & Hoffman, 1993; Duncan, Humphreys & Ward, 1997; Stuyven et al., 2000). A role of attention in saccade tasks that has been well known happens when performance of a saccade requires visual attention to be disengaged from the current target and transferred to the new fixation point (Crawford & Muller, 1992; Crawford et al., 2011). Van Stockum et al. (2011) measured mean latency of saccades when subjects were required to perform a discrimination task for saccadic targets and reported that saccadic latency increased with visual distracters added to the discrimination task. As explained above, the discrimination task in our dual task could increase the level of visual attention and facilitate saccade execution. Hence, it did not count as an irrelevant concurrent task. In contrast, saccade latency increased when we introduced the mental arithmetic task, which was similar to the distracter used by Van Stockum et al. (2011) in that it was irrelevant to the task, and hence it increased saccade latency. Withdrawal of visual attention by a secondary task can interfere with execution of reflexive saccades and result in increased
latency of prosaccades (Kristjánsson et al., 2001). Overall, the longer saccade latency in the presence of the arithmetic task as found in this thesis agreed with previous findings indicating that execution of prosaccades can be delayed when another concurrent task has disrupted the visual attention paid in the saccade task (Pashler et al., 1993; Roberts et al., 1994; Duncan et al., 1997; Stuyven et al., 2000; Kane, Bleckley, Conway & Engle, 2001; Kristjánsson et al., 2001; Montagnini & Chelazzi, 2005; Irving et al., 2009; Guyader et al., 2010).

We performed additional analysis of the latency of saccades to investigate the sources of the changes in them. This included investigating various categories of saccades and conducting LATER model analysis of saccade latency. Before discussing our findings, we will explain the neural resources that could be used during our saccade experiment, more specifically the restricted triple task, below.

Similar dorsal and ventral pathways identified in visual processing, the attentional system, and language processing have been suggested to mediate mental arithmetic (Klein, Moeller, Glauche, Weiller & Willmes, 2013). Neural structures involved in arithmetic tasks play a key role in oculomotor movements. Parietal circuits involved in mental arithmetic contribute to the spatial coding associated with saccades (Knops, Thirion, Hubbard, Michel & Dehaene, 2009). The neural network used to support mathematical thinking requires close interplay with and widespread activations of various parts of the brain including frontal and prefrontal cortex, cingulate cortex, occipital cortex, frontoparietal connectivity, and particularly the parietal cortex (Dehaene & Cohen, 1995; Kong et al., 2005; Klein et al., 2013). Posterior parietal cortex has been thought to be involved in both calculation and also all visuo-spatial tasks such as spatial attention and saccade (Corbetta & Shulman, 2002; Hubbard, Piazza, Pinel & Dehaene, 2005). Attentional shifts and eye movements share similar neural mechanisms (Kustov & Robinson, 1996; Simon et al., 2002). Concurrent tasks with prosaccades demand a higher level of attentional resources to perform the saccades than doing the saccade task alone. It has been found that signals from the frontal eye fields to generate saccades can be delayed when the task performer does an irrelevant concurrent task with saccades (Pashler et al., 1993).

The amount of interference with prosaccade latency caused by irrelevant concurrent tasks has been explained in terms of the capacity of the executive controlling system. More executively controlled saccades, as opposed to those that are performed automatically, are more vulnerable to a cognitive interference effect from secondary tasks, and therefore an increase in latency
Studies in which antisaccades were investigated have shown less suppression of reflexive saccades, which are generally executed by the superior colliculus when cortical control of saccades is weakened. Less cortical control on saccade execution could contribute not only to a higher error in antisaccade tasks, but also could increase the number of incorrect prosaccades with shorter latencies, resembling patterns observed in patients with frontal lobe lesions (Roberts et al., 1994; Halliday & Carpenter, 2010). Although using a mixed antisaccade and prosaccade task found that mental arithmetic interfered with antisaccades, no increases in latency of correct prosaccades was found, possibly due to less cortical control being needed to generate correct prosaccades rather than to generate antisaccades (Roberts et al., 1994). Our return trials showed more fast-regular saccades with shorter latency as compared to target trials, where more regular saccades and fewer fast regular saccades were recorded under mental load. The current findings can be explained in terms of a higher level of controlled execution for regular saccades as compared to fast regular saccades, resulting in decreased numbers of fast regular saccades and increased numbers of regular saccades for the triple task. Return trials were predictive and did not require as much controlled execution of saccades; this could result in more fast regular saccades and shorter latency for (fast) regular saccades when compared to target trials.

Central executive capacity depends on both task demands and the difficulty level of information processing. Individual differences in controlled execution of saccades can be explained in terms of the available capacity of working memory and controlled attention to the task demands (Roberts et al., 1994; Kane et al., 2001; Irving et al., 2009). Irving et al. (2009) compared saccade latencies during a mixed saccadic task that included prosaccades and antisaccades. The task was performed by both children and adults; the adults performed the task whilst also doing number repetition and subtraction. The results showed no significant effect of the dual task on the adult group in terms of either error rate or latency for both prosaccades and antisaccades; however, the findings for the children indicated that the process of decision-making increased the latency of prosaccades. The simultaneous combination of decision-making and saccade execution could result in the failure to respond appropriately, including both higher response errors in antisaccade task and longer prosaccade latencies (Irving et al., 2009). A previous study by Mitchell et al. (2002) investigated the effects of different levels of a memory
task (the n-back task) on saccadic latency. The saccade task was a mixture of both antisaccades and prosaccades. The results showed working memory increased the latency of correct saccades. However, there was no systematic correlation between an increase in saccadic latency and a higher level of task difficulty. An increase in saccade latency in the presence of a secondary task has also been found for endogenously generated saccades (Hoffman & Subramaniam, 1995; Kowler et al., 1995; Deubel & Schneider, 1996; Kristjánsson et al., 2001). These results suggested that conscious behavioral intention to monitor or maintain some concurrent mental activity can affect the saccade onset through a cortical control system when the saccade task is in conflict (or opposition) with the behavioral goals of the task performer (Mitchell et al., 2002). Control of the supervisory attentional system on overlearned responses can explain interfered execution of prosaccades by another task such as an arithmetic task. A mind distracted with a concurrent mental task can result in behavioral lapses; this is similar to the delay in saccade execution in our triple task. Control of overlearned responses has been described as depending upon a supervisory attentional system, which, for example, allow a driver to decide to delay passing or not passing a street during a green light if a pedestrian is still standing on the road (Mitchell et al., 2002).

Fronto-executive load can happen when a secondary task puts a heavy load on working memory, and the current goals conflict with the prepotent behavioral tendencies. Similar to when there is little or no task demand, the fronto-executive load has been found to decrease the controlled processing of saccades and increase reflexive responses (Roberts et al., 1994; Jonides, Smith, Marshuetz, Koepp & Reuter-Lorenz, 1998; Mitchell et al., 2002; Irving et al., 2009; Halliday & Carpenter, 2010). Thus, we expected an increase in the saccades with short latency, i.e. in the range of express saccades. Instead, the changes in saccade reaction time found in our study were mainly related to the changes in (fast) regular saccades, indicating that our subjects were not placed under heavy workload conditions. Instead, the arithmetic task in our experiment resulted in interference with the controlled saccade executions, thus leaving prosaccades with a longer latency. Besides affecting working memory and the capacity of resources allocated to cover task demands, task context also contributes to the variations in the proportions of various saccades under a concurrent task (Halliday & Carpenter, 2010). Hence, another contributing factor to finding no significant change in the proportion of express saccades across our tasks might be due to task context; e.g. absence of antisaccade or no-go trials in our experiment.
No systematic correlation has been shown between working memory capacity and controlled execution of saccades (Roberts et al., 1994; Mitchell et al., 2002; Halliday & Carpenter, 2010; Crawford et al., 2011). The capacity of working memory not only plays an important role in task performance, but also produces individual differences. How much working memory has been allocated for the task demands can vary across individuals (Vogel, McCollough & Machizawa, 2005). The level of selective attention and effort allocated to cover the task demands indicates the importance of the task to the performer; this is also true for controlled execution of saccades (Awh, Vogel & Oh, 2006; Fougnie, 2008). Similar to the volitional control of saccade execution to manage task demands, unconscious control of saccade execution can result in making the saccade prevail over the other task (Reddi & Carpenter, 2000; Mitchell et al., 2002; Montagnini & Chelazzi, 2005; Guyader et al., 2010). As explained in the previous chapter, in some circumstances, it might be better to delay or reject a saccade so as to defer its cost (Guyader et al., 2010). The urgency of saccade motor preparation can be altered by changing the rate and variability of the underlying decision signal (Montagnini & Chelazzi, 2005; Guyader et al., 2010). To achieve this, prior to any saccade, visual sensory information (bottom-up) needs to be integrated with cognitive (top-down) influences (Schall & Thompson, 1999). Our results showed saccade latency increased with mental arithmetic, a task that has been known to involve the working memory system (Logie, Gilhooly & Wynn, 1994; DeStefano & LeFevre, 2004). We asked our participants to keep counting backwards as they completed the saccade task. Subjective and physiological tests indicated higher mental workload for all of the participants under the triple condition. No clear priority was assigned to either the counting or saccade tasks for our participants. No feedback was provided for the tasks, and subjects’ performance on the arithmetic task was also not controlled. Since the level of saccade urgency could delay or facilitate saccade execution (Pashler et al., 1993; Duncan et al., 1997; Reddi & Carpenter, 2000; Stuyven et al., 2000; Kristjánsson et al., 2001; Reddi et al., 2003; Montagnini & Chelazzi, 2005), our finding of a delay in saccade execution with mental arithmetic might be due to task priority. It was possible that assigning a higher priority to the arithmetic task resulted in postponed saccade execution. Hence, saccade latency might have increased as a cost of prioritising the arithmetic task; this was a possibility because our participants were more inclined to do the arithmetic task than saccades. The possibility of the importance of the saccade task being lower than the arithmetic task was increased as our participants were not receiving feedback for the
post-saccadic task. Although they were encouraged to keep counting back during the triple task, there was a possibility of changes in priority of saccade execution in the presence of an arithmetic task. Another possibility was that limited available resources for information processing with the concurrent task resulted in slower information processing. These possibilities could be tested by fitting a line to the data in the LATER model of latency distribution. In the LATER model of latency distribution, the linear regression line swivels in the case of changes in urgency and shifts in case of changes in the information supply (Reddi & Carpenter, 2000; Reddi et al., 2003). There was a possibility of task switching or change in priority and criterion level of the saccade task over the arithmetic task if our results showed that swivel was favoured over shift (Reddi & Carpenter, 2000; Sinha et al., 2006). In contrast, our results showed a shift in the LATER model latency distribution. Thus, we accepted our hypothesis indicating that changes in saccade latency were due to the changes in information supply for the saccade decision signal. The smaller $\mu$-value found for the triple task than the other tasks strengthened the likelihood that the longer saccade latency found resulted from slowness in information processing (Reddi et al., 2003). Changes in saccade latency through changes in the saccade decision signal can represent interference with the attention allocated to the saccade target (Harwood et al., 2008). As mentioned previously, similar resources have been known to be used for arithmetic, discrimination, and saccade tasks (Recarte et al., 2008). Saccade execution could be delayed in the presence of limited capacity resources available for information processing. Using the arithmetic task as a concurrent irrelevant task could limit the speed of elevation in the decision signal to reach the threshold required for saccade execution. The slower manipulation of the information indicated by smaller $\mu$-values in the LATER model could lead to a longer time taken to generate saccades (Reddi et al., 2003) and result in prolonged saccade latency for our triple task. In other words, longer latency of saccades in the presence of a slower rate of rise in the saccade decision signal could indicate a decline in the cortical signals for saccade generation, especially in frontoparietal regions (Ikeda & Hikosaka, 2003; Montagnini & Chelazzi, 2005); this was due to the cognitive load induced by concurrent mental arithmetic.

Regardless of task conditions, initial saccades would not always take the eye onto the desired target and secondary saccades might be required for target acquisition (Weber & Daroff, 1972). In the next section, we have discussed our findings for the effects of mental load on secondary
saccades, and have explained how changes in latency of saccades can influence the production of secondary saccades for target acquisition.

4.3.3. Secondary saccades and target acquisition time

Centripetal saccades that bring the eyes back on a target at the primary gaze position have been known to be more accurate than centrifugal saccades that move the eyes towards a target located at an eccentric position. This might be due to the ease of the task and perception of a known target position that was always the primary position for return trials (Kapoula & Robinson, 1986). Knowledge of the target location can affect the gain of the initial saccade and the frequency of secondary saccades in a task (Henson, 1979). In our experiment, participants were instructed always to look back to primary position. Thus, secondary saccades were reduced for return trials as compared with target trials, possibly due to the knowledge of the target location. It was unlikely that knowledge of target position was a confounding variable in our target trials as the target locations were randomised.

It has been shown that amplitudes of saccade undershoots and secondary saccades increase (roughly from 10% to 14%) when a saccade task is accompanied by a discrimination task. However, the overall accuracy of the saccade task does not necessarily improve when accompanied by a discrimination task (Kapoula & Robinson, 1986). This is in agreement with our finding indicating that the gain of initial saccades decreased for target trials in the dual task, while the accuracy of final saccadic end position did not differ across task conditions. It has been suggested that saccade undershoots occur to avoid a biological noise, which is proportional to the motor command, at a cost of the optimal gain of initial saccades (Harris & Wolpert, 1998; Toyomura & Omori, 2003; Tsimring, 2014). However, the detail of this biological noise has remained as yet unclear and is out of the scope of this thesis. Harris (1995) suggested a model in which saccade undershoots minimise the total saccadic flight time rather than retinal error during saccade sequences. However, a later model proposed by Toyomura and Omori (2003) suggested that saccade undershoots can be a tradeoff between flight time and accuracy of saccadic end position while both total flight time and accuracy of the saccade task can be increased. We measured increased target acquisition time and saccade undershoots for target trials in the dual task, with no change in final saccadic end position between tasks. These findings are consistent with the possibility of a tradeoff between total flight time and accuracy as suggested by
Toymura and Omori (2003). Considering total flight time as the sum of durations of consecutive saccades and latency of each secondary saccade, it seems that total flight time tended to increase for target trials during the dual task as compared to the other tasks. Our findings of similar final saccadic end position across tasks agreed also with Kapoula and Robinson (1986) who suggested that more secondary saccades do not necessarily improve accuracy. Fewer secondary saccades during the arithmetic task might be due to our participants being less attentive towards the discrimination task in the presence of mental arithmetic. Thus, our results for the dual task agreed with previous studies indicating that discrimination tasks lead to larger saccade undershoots, while more secondary saccades increase total flight time with no change in final saccade end position (Kapoula & Robinson, 1986; Toyomura & Omori, 2003). Overall, we suggest the cumulative effect of increased total flight time might result in target acquisition time increasing for target trials in the dual task as compared with the single task.

Importantly, the effects of the task which led to an increased saccade latency and target acquisition time cannot be explained in terms of post-saccadic visual demand, since changes in saccade latency and target acquisition times were not limited to the target trials during which the discrimination task was required to be performed. We found task significantly affected occurrence of secondary saccades during target trails; i.e. more secondary saccades recorded during the dual task than the triple task. Below, a possible reason for this finding has been discussed.

Secondary saccades are generated based on both afferent input, i.e. retinal signals, and the error in endpoint position of initial saccade which is already derived from efference copy, i.e. a feedforward signal of the saccade motor command (Becker & Fuchs, 1969; Collins, Rolfs, Deubel, & Cavanagh, 2009). Efference copy signals are generated before onset of saccades and are used for saccade remapping, i.e. updating the retinal coordinates of intended visual targets, (Sperry 1950, Colby & Golberg 1999). The type of signals that efference copy might use to drive saccade remapping is not yet clear and might include forwarded copies from the saccade-related burst signal (Quaia et al. 1998), from both eye position and velocity information (Medendorp et al. 2003), and/or from eye velocity information alone (Droulez and Berthoz 1991). Most likely, various combinations of the saccade-related signals may be used in different brain areas (Keith, Blohm & Crawford, 2010).
Efference copy is associated with several neural pathways such as superior colliculus to frontal eye field via thalamus (Collins 2010). Brain areas associated with saccade programming, including the superior colliculus, frontal eye fields, and parietal cortex, show activity across saccade remapping (Mays and Sparks 1980; Duhamel et al. 1992; Walker et al. 1995; Umeno and Goldberg 1997). It has been reported that frontal eye fields are involved in predictive remapping of saccades, defined as when the efferent copy is used shortly before the saccade execution in order to optimise post-saccadic position (Umeno & Goldberg 2001; Sommer & Wurtz 2006). Updating the location of the saccade target has been reported to activate the parietal cortex. This was identified both by measuring blood oxygen level (Merriam et al. 2003) and by applying transcranial magnetic stimulation which disturbed information processing over the parietal cortex (Morris et al., 2007). The results of a saccade task in human adults with focal lesions of the cortex, including frontal eye field, dorsolateral prefrontal cortex, supplementary motor area, and posterior parietal cortex, showed that lesions of the posterior parietal cortex interfered with the accuracy of secondary saccades with no effect on the first saccade (Heide and Kompf 1998). In contrast, both initial and secondary saccades showed normal accuracy in the presence of focal lesions of the prefrontal cortex (Duhamel et al. 1992; Heide et al. 1995). Katschmarsky and colleagues (2001) suggested that the posterior parietal cortex uses efference copy of the initial saccade to construct the secondary saccade. In the presence of a deficiency in efference copy, as seen in such patients with focal parietal lesions, we expected an increase in the error in final saccadic eye position (Maruff, Wilson, Trebilcock, Currie. 1999; Zhai & Enderle 2016). Our results showed no significant difference between tasks for final saccadic eye position, albeit the ratio of secondary saccades significantly reduced under the high load. One possible reason for our findings might be predictive saccade remapping as explained below.

By using efference copy from the initial saccade, the magnitude of the error in the landing position of the initial saccade can be anticipated before the execution of the initial saccade (Goldberg, Colby & Duhamel 1990). By calculating the potential error in sensory outcome, an optimal action can be selected for the initial saccade; this process is named predictive saccade remapping (Becker & Jürgens 1979; Baizer & Bender 1989; Wolpert 1997; Ray, Schall & Murthy 2004). Whereas the programming of initial and secondary saccades are parallel, saccade remapping may result in longer latency of the initial saccade (Zhai & Enderle 2016). We found longer saccade latency and no change in final saccadic end position under high mental load. Our
results are consistent with Zhai & Enderle (2016) for longer latency of the initial saccade as the cost of predictive saccade remapping. Both our triple and dual tasks, i.e. high and low mental loads, required subjects’ responses and were expected to increase secondary saccades more than the single task. However, we recorded fewer secondary saccades under high mental load when the available resources for information processing are typically limited. For the high mental load condition, our subjects were required to perform saccades concurrent with the arithmetic task. Both the frontal and, to a greater extent, parietal cortex are involved in arithmetic tasks (Knops et al., 2009). Recarte and Nunes (2003) suggested that visual processing time tended to decrease under high mental load; e.g. blinks are inhibited to increase the efficiency of target viewing time. In agreement with Recarte and Nunes (2003), for efficient visual processing time with high load, it seems that initial saccades tended to be more optimal in accuracy under high load as compared to low load. Possibly, mental load may affect final saccadic eye position through predictive remapping of initial saccades, which would increase the accuracy of initial saccades and decrease generation of secondary saccades. This process is also in line with the tradeoff between total saccade flight time and accuracy of final saccade end position explained formerly in this section.

5. **Summary and conclusion**

We conducted acuity and saccade experiments in normal participants. The aim of the acuity experiment was to ascertain that restricted viewing time and concurrent mental arithmetic can induce mental stress within subjects. Comparing subjective and physiological measures of mental load i.e., heart rate, pupil size, and skin conductance level across tasks and within subjects confirmed that stress was induced in the restricted dual task. We then were confident that a similar experimental protocol could be used with the participants with infantile nystagmus syndrome (INS) to investigate the effects of mental stress on INS. The next chapter explains in detail the experiments involving participants with INS.

Using three levels of task difficulty in our saccade experiments showed significant changes in latency of prosaccade due to changes in task demands. The size of the E target used in our saccade tasks was above subjects’ visual acuity threshold and easy to recognise, possibly
resulting in the visual task alone not being able to induce a high amount of cognitive load within participants. Our results are consistent with the assumption that the latency of prosaccades is not influenced by minor changes in the level of task demands and cognitive load, but it can be changed by interference in the controlled execution of saccades in the presence of a disruptive secondary task. We believe an increase in saccade latency plays a main role in delaying target acquisition; however, the combined effects of saccade latency and total flight time can increase target acquisition time.

There was a possibility of a tradeoff between speed of saccade execution and accuracy of performance doing the tasks with mental arithmetic. However, our results obtained from the LATER model showed a shift rather than swivel in the latency distribution line. Moreover, we did not find any change in final saccadic end position or accuracy of manual responses across tasks. Due to the above findings, our results have rejected the possibility of a conscious tradeoff between speed of saccade execution and accuracy of task performance (Reddi & Carpenter, 2000). Instead, our results from the LATER model confirmed that controlled execution of saccades, in the presence of limited resource capacity available for information processing, was responsible for the longer saccade latency, and hence target acquisition time, in the presence of the arithmetic task.

A mental distraction by an irrelevant task, i.e., arithmetic, slowed saccade execution and increased target acquisition time. It seems that mental load, rather than a shortage of visual processing time, degraded the accuracy of responses in the discrimination task. A slow rate of rise in the saccade decision signal results in longer saccade latency, and hence longer target acquisition time can increase. Slowed target acquisition can be critical in terms of task performance in daily life when both accuracy and speed can be required to deal with visual targets under high mental load such as when driving.

We can conclude that the triple task induced high cognitive load in normal participants, and hence it was reasonable to use it to induce a high mental load in our INS group by instructing them to perform an arithmetic task at the same time as a saccade task. As explained before, patients with INS have reported both the degraded quality and the lower speed of seeing objects; these refer, respectively, to how well and how fast they can see visual objects (Sprunger et al.,
1997; Wang & Dell'Osso, 2007a). Knowing this, we aimed to investigate to what extent individuals with INS see more poorly (i.e., have degraded vision for resolving target details) and see slower (i.e., display degraded timing of the visual system) compared to the control group with and without mental load. We have used a similar task protocol described in the current chapter for participants with INS, with more details explained in the following chapters. We ran two experiments in the INS group, including an acuity experiment and a saccade experiment. Details pertaining to each of them are explained in the following two chapters.
Chapter four: Acuity experiment in INS group

1. Background and aim

It has frequently been claimed that nystagmus worsens in response to psychological factors such as tiredness, anxiety, and the attention level of individuals with INS (Dell'Osso et al., 1974; Dell'Osso, 1982; Abadi & Dickinson, 1986; Abadi & Scallan, 2000; Abadi & Bjerre, 2002). However, studies that investigated the effects of internal states on INS have shown inconsistent results (Abadi & Dickinson, 1986; Tkalcevic & Abel, 2005; Wiggins et al., 2007; Cham et al., 2008b; Jones et al., 2013). Tkalcevic and Abel (2005) did not find any changes in INS parameters due to increased visual demand, that is when target visibility is reduced, and suggested INS is affected by the importance of visual task to the performer. In contrast, Wiggins et al. (2007) found that the intensity of nystagmus decreased, and foveation increased with visual demand. Their findings showed that nystagmus improved when effort to see was required due to reduced target visibility. Cham et al. (2008b) found that in the presence of task-induced stress, foveation time decreased under high visual demand compared to low visual demand. Studies comparing relaxed and stressed conditions have shown deterioration of both INS parameters and manual response times when stress or task difficulty were increased; however, the results for visual acuity have been inconsistent (Yang et al., 2005; Cham et al., 2008b; Jones et al., 2013). Time restriction has been shown to reduce visual acuity in INS and that reduction varied across gaze positions (Yang et al., 2005). While the nystagmus waveform typically appears to allow for the best vision at the null (Gresty et al., 1984; Hertle & Dell'Osso, 2013b), there is a possibility that the effects of increased mental load on INS could vary with gaze, as there is more scope for deterioration at the null than at some distance away from it. Moreover, the studies of internal states and task demands on INS eye movements have been limited to null or primary position only (Tkalcevic & Abel, 2005; Wiggins et al., 2007; Cham et al., 2008b; Jones et al., 2013). Since looking at various gaze positions is necessarily required under real world conditions, the assessment of visual function in patients with INS should be done across various gaze positions. In the real world, visual tasks may be carried out while also experiencing a mental load; that is,
when a person is working harder and expending more energy to meet task demands (Eggemeier, 1988). An example would be someone trying to read a faded road sign in bad lighting when driving to an important meeting behind schedule. We aimed to address whether or not the same changes in task demands have differing effects on INS and on vision both at and away from the null position.

2. Methods

2.1. Sample size

We calculated the average of changes in foveation which have been reported by the previous studies investigating the effects of mental stress and visual acuity demand within INS subjects. Using the results reported by Cham et al., (2008) and Wiggins et al., (2007), we calculated the average percentage change in foveation time within subjects due to the task condition as 10.59. Similarly, we calculated the average standard deviations of within subjects’ differences reported by the above studies as equals to 9.12. Using G*Power software, with a required within-subjects mean difference of 11 units and standard deviation of 9, the power of 95% and alpha of 5%, the sample size was 11. This calculation was based on a paired t-test between two conditions e.g., the high mental load condition compared to the baseline condition. Therefore the current study was suitably powered to detect the minimum required mean difference of 11 units in the main effects, 2-way and 3-way interactions, if the number of participants were eleven subjects or more.

2.2. Participants

Twenty-two individuals with horizontal infantile nystagmus volunteered for this study. The participants were recruited from a referring ophthalmologist. The ophthalmologist examined the patients for any other detectable ocular pathology in addition to nystagmus. The nystagmus waveforms were investigated with eye movement recording conducted by the examiner. Seven
participants were excluded on the basis of eye movement recordings, including three participants with congenital periodic alternating nystagmus, and another four who were diagnosed with fusion maldevelopment nystagmus syndrome (details will be provided below).

Fifteen adult participants with idiopathic INS remained to participate in the study (six female and nine male; mean age ± SD: 28.4 ± 15.5 years). Clinical data for the remaining fifteen participants are shown in Table 1. All volunteers were requested to avoid alcohol on the night before the test and were required to wear their habitual optical corrections during the tasks, if they had any.

2.3. Procedures

All procedures used in the current experiment in the INS group are identical to the procedures used in chapter 3 for the acuity experiment with normal participants, with the exception of some important differences explained below in detail.

2.3.1. Calibrating eye tracker

The method used to calibrate the eye tracker for participants with INS was similar to the method used to calibrate it in the normal group as explained in chapter 3, section 2.2.1, but with two important differences. First, the eye tracker was calibrated using five horizontal and vertical points (HV5), presented at the central gaze position, ±25° horizontally away from the centre, and ±5° vertically away from the centre. Second, fixation duration was reduced to the minimum value considered valid in the eye tracker software. It allowed the examiner to run the calibration by modifying the minimum duration for a valid fixation using the related *.ini file from the EyeLink host computer. The minimum fixation duration could be initially set up based on previous records in our lab for the same participant. Alternatively, the minimum duration for a valid fixation was decreased to a number selected by the examiner (e.g., 150 msec, based on Figure 5 of the study by Jones et al. (2013). If a participant with INS still failed to show stable fixation, the valid duration could be decreased even more, e.g., to 100 msec, 50 msec, etc. Using this method, the eye tracker was calibrated for each participant individually.
Table 1: Clinical characteristics of the individuals with idiopathic INS who participated in the study, along with the size and contrast of the target at which task performance plateaued under low and high mental load conditions.

<table>
<thead>
<tr>
<th>Part.</th>
<th>Null</th>
<th>Waveforms</th>
<th>Habitual correction</th>
<th>Eye tested</th>
<th>Visual acuity</th>
<th>LogMAR size (%Contrast) of the last presented target at the study which was identified by the participant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>With low mental load</td>
</tr>
<tr>
<td>1</td>
<td>0°</td>
<td>JL</td>
<td>R: Plano</td>
<td>L</td>
<td>R: 6/4.5</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td></td>
<td>-20°</td>
<td>Jef</td>
<td>R: -3.00/-3.75×165°</td>
<td>L: -3.25/-3.50×25°</td>
<td>R: 6/7.5</td>
<td>Null: 1.1 (5)</td>
</tr>
<tr>
<td>2</td>
<td>++25°</td>
<td>PCL, JLf</td>
<td>R: Plano</td>
<td>L: Plano</td>
<td>R: 6/6</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>3</td>
<td>+5°</td>
<td>P, DJR, PCL</td>
<td>R: +4.00/-0.50×140°</td>
<td>L: +4.25/-2.25×143°</td>
<td>L: 6/24</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>4</td>
<td>+5°</td>
<td>Pfs, PC</td>
<td>R: Plano</td>
<td>L: Plano</td>
<td>R: 6/18</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>5</td>
<td>0°</td>
<td>Jef</td>
<td>R: +5.00/-5.00×180°</td>
<td>L: +4.00/-4.00×180°</td>
<td>R: 6/15</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>6</td>
<td>-20°</td>
<td>Jef</td>
<td>R: -1.50/-1.25×5°</td>
<td>L: -0.75/-1.25×175°</td>
<td>R: 6/7.5</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>7</td>
<td>-20°</td>
<td>Jlf</td>
<td>R: -1.50/-1.25×5°</td>
<td>L: -0.75/-1.25×175°</td>
<td>R: 6/7.5</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>8</td>
<td>+20°</td>
<td>BDJ, AP</td>
<td>R: -1.00/-2.00×145°</td>
<td>L: 0.25/-2.00×05°</td>
<td>R: 6/24</td>
<td>Null: 1.1 (50)</td>
</tr>
<tr>
<td>10</td>
<td>0°</td>
<td>PPfs</td>
<td>R: Plano</td>
<td>L: Plano</td>
<td>R: 6/9</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>11</td>
<td>++25°</td>
<td>DJ</td>
<td>R: +6.75/-1.00×180°</td>
<td>L: +6.00 sph</td>
<td>R: 6/24</td>
<td>Null: 1(2)</td>
</tr>
<tr>
<td>13</td>
<td>++25°</td>
<td>JLf</td>
<td>R: -0.50/-1.00×90°</td>
<td>L: -0.50/-1.00×88°</td>
<td>R: 6/24</td>
<td>Null: 1.3 (50)</td>
</tr>
<tr>
<td>14</td>
<td>-5°</td>
<td>DIR, Pfs</td>
<td>R: -0.50/-3.25×90°</td>
<td>L: -1.50/-2.00×90°</td>
<td>L: 6/48</td>
<td>Null: 1.65(50)</td>
</tr>
</tbody>
</table>

All measurements and eye movement recordings were done with the participants’ habitual correction. Part., Participants’ code; Null., null position; -15° away., 15° to the left of the null; +15° away., 15° to the right of the null; LP., light perception only. Nystagmus waveforms are jerk (J), dual jerk (DJ), pseudocycloid (PC), jerk with extended foveation (Jef), Pendular with foveating saccades (Pfs), Bidirectional jerk (BDJ), Asymmetric pendular (AP), and pseudopendular with foveating saccades (PPfs). R and L refer to right and left eyes. Eye tested refers to the eye which was tested for the current study.; 1: Participant has retinal arterial occlusion in left eye which was persisted for a long time.; 2: participant has missing data for high visual demand level at the null position under high mental load.; 3: Due to lapsed responses, the participant has missing data for high visual demand level at 15° away position under high mental load.; 4: Due to lapsed responses, the participant has missing data for low and high visual demand at 15° away position under low mental load.
Similar to the procedure for the normal group, the examiner manually accepted each point identified as a fixation by the EyeLink II software until a cross pattern for the calibration grid was displayed on the screen of the EyeLink II host computer. The examiner repeated this procedure until a reasonably symmetric cross was displayed and the accuracy of the calibration was better than 0.5°. After this initial calibration of eye position, we scaled data off-line for each eye using the baseline task explained below.

**2.3.2. Baseline task (Calibration run)**

Baseline measures for INS parameters, pupil size, heart rate, and skin conductance level were recorded during calibration runs that were conducted before the acuity tasks. The procedure used for the baseline task was identical to the procedure described for the baseline task in normal participants (see section 2.2.2 in chapter3). Patching did not change the nature of nystagmus for any of the participants; that is, there was no latent component.

As for the normal group described in chapter 3, section 3.2, raw horizontal eye position was scaled off-line for each eye in the baseline task (calibration run). For each location, multiple instances of when the eye appeared to be foveating the target were chosen. Localisation of potential foveations was done based on the foveation strategy of INS waveforms described by Dell'Osso and Daroff (1975). The locations of the consecutive potential foveations needed to fall at nearly the same gaze position in the plot of eye position. Similar to what was done for the normal group in chapter 3, the best fitted linear regression line was then used to scale all subsequent data. Eye velocity was calculated digitally as the first derivative of position with respect to time (Glasauer, Hoshi, Kempermann, Eggert & Büttner, 2003). Figure 24 shows an example of the baseline task before and after the scaling of horizontal eye positions were converted from pixels to degrees.
Figure 24: Illustrations of a segment of the recording obtained during the baseline task in a subject with INS displayed in MATLAB before (a) and after (b) horizontal eye position was rescaled off-line. Red, green, and blue lines refer respectively to target location, eye velocity, and horizontal eye position that were plotted versus time. Here the right eye is shown.

Since the baseline task presented targets on known locations, the examiner could be convinced that the calibration remained valid after the *.ini file was modified for each subject.
(see figure 25 for an example). Then, we determined foveation using the criteria of eye velocity \( \leq 4 \text{ deg/sec} \) and eye position within \( \pm 0.5^\circ \) of the target for the study, as explained further in the following sections. The gaze position with the least INS intensity during calibration was determined as the null position (Hertle & Dell'Osso, 2013b).

![Figure 25: Illustrations of a segment of the recording obtained during the baseline task in a subject with INS displayed in MATLAB. Red, green, and blue lines refer respectively to target location, eye velocity/40, and horizontal eye position that were plotted versus time. Here the right eye is shown.](image)

3.2.3 Test for periodic alternating nystagmus (PAN)

Periodic alternating nystagmus was tested for before the tasks by monitoring nystagmus direction during a four-minute fixation task with both eyes viewing. The recording was continued for another two minutes if the participant momentarily became inattentive. The duration chosen was a compromise between spotting a direction reversal, indicating the presence
of congenital PAN, and not further lengthening an already long experiment. The duration of congenital PAN is generally 4 minutes; however, it can be as long as seven minutes and there is no foolproof cutoff to use to ensure the absence of congenital PAN (see Shallo-Hoffmann and Riordan-Eva (2001) for review). According to Gradstein et al. (1997), recording nystagmus for at least 3 minutes is necessary to diagnose PAN. It is worth to not the examiner inspected the recordings manually to select the data sections to analyse (see following section). Thus, the examiner could detect PAN reversals during this inspection, if she failed to see it during the 4 or 6 minutes fixation task.

2.3.3. Acuity experiment

Similar to the experiments with normal participants described in chapter 3, the experimental protocol for participants INS included a baseline task, an acuity task with unrestricted viewing time (that imposed only a low mental load), and an acuity task with time restriction and concurrent mental arithmetic (that imposed a high mental load). These constituted the baseline, low mental load, and high mental load conditions, respectively. Chapter 3, section 2.2.5, provides more details for the acuity experiment. It should be noted that this experiment, while referred to as the “acuity experiment,” does not formally assess changes in visual acuity under differing task demands, as the projector available at the time of data acquisition was unable to produce sufficiently small optotypes.

2.4. Apparatus

In addition to eye movement recording used to measure INS parameters, a retrospective subjective scale and concurrent physiological measurements were recorded to confirm variations in perceived mental workloads across the tasks (see chapter 3, section 2.2.6). The apparatus used for the experiment in INS was the same as the apparatus used for normal participants explained in chapter 3, section 2.3.
3. Data preparation

The data recorded during the experiment were horizontal eye positions. The INS parameters were calculated by the examiner after participants completed all tasks. The method used to measure heart rate and mean skin conductance level for each task was the same as described in chapter 3, section 3.1.1. As with normal participants (explained in chapter 3), task performance in participants with INS was also defined for each gaze position and acuity task as the size and contrast of the last optotype that was correctly identified by the participant.

Our experimental protocol and data analyses for the acuity experiment in INS are similar to the method used by Cham et al. (2008b). For each of the acuity tasks, INS parameters were evaluated at low and high levels of visual demand. Visual demand was defined based on the visibility difficulty, which was increased by presenting the targets at smaller sizes and lower contrasts. Low visual demand served to present an easy visual task while high visual demand targets increased the difficulty of target recognition. Real-world examples of low and high visual demand targets would be a faded road sign with small text versus a large print, black and white one. The two smallest and lowest contrast targets identified by the participant were referred to as requiring high visual demand. This was identified from the plateau during the final run of reversals for each task condition and gaze position. The two largest targets at the highest contrast viewed by the participant were referred to as requiring low visual demand.

The data recorded at each task condition were inspected by the examiner for blinks or any recording artifacts, such as the loss of tracking or the subjects’ momentary disengagement from task (i.e., they looked away from the target or appeared in the recording to be inattentive, indicated as when extended slow phases drifted to one side and no foveating saccade was produced). These were not included in the sections selected for analysis (Abel, Wang & Dell'Osso, 2008). The examiner then selected the sections for analysis for each task by manually placing cursors at the beginning and end of the intervals that included continuous periods of nystagmus, which were as long as possible; that is, uninterrupted by blinks or data drop-outs. These intervals could then be combined for each gaze position and task condition; and INS parameters were measured by calculating the means of them across the selected intervals. Recording artifacts in some trials and also the dependence of trial length upon participants’
responses and on the task being run, resulted in the length of the intervals selected for data analyses varying between participants and between tasks in our study.

The percentage of time per INS cycle for which foveation criteria (eye velocity \(\leq 4\ \text{deg/sec}\) and eye position within \(\pm 0.5^\circ\) of the target) were satisfied was used as the percent foveation time. INS amplitude was measured as the mean of the distances between peaks and troughs of INS cycles, and frequency was calculated as the number of INS cycles per second. Pupil area was measured only during foveation periods (see also chapter 3, section 3.1.2).

### 4. Statistical tests

For INS parameters and workload measurements, the analysis was conducted on the collected data using IBM SPSS Version 20 and GraphPad Prism Version 5 for Windows. The general methods used for statistical tests were the same as those used with the group of normal participants as explained in chapter 3, section 4. For INS parameters, heart rate, pupil size, and skin conductance, the normality assumption appeared justified. For normally distributed data, there was insufficient evidence to reject the assumption of homogeneity of variance. In cases where sphericity could not be assumed, Greenhouse-Geisser corrections were used. Similar to the previous chapter, we corrected p-values for multiple tests by Bonferroni correction.

One-way repeated measures ANOVAs were used to evaluate the effects of mental load on heart rate, MTE score. Repeated measures ANOVAs were used to evaluate the main effects and interactions effect of mental load, visual demand, and gaze position on each INS parameter; these were percent foveation time, amplitude, frequency and intensity of nystagmus. One independent variable was evaluated at a time. Two gaze positions were included in the analyses: at the null and 15° away from it, either to the left or to the right. These locations were chosen to ensure that analyses could be performed at the null and at a uniform distance, as far away from the null as possible, for the maximum number of participants. For participants with nulls near the centre, locations further from the null sometimes exceeded the linear range of the recording. Even with a maximum of 15° away from the null, repeated measures analyses were only possible with 11 participants for whom data were available at these positions (see Table 1). Data were
excluded from analysis due to reasons such as poor recording, blinks, or head movements. If the data for both \(15^\circ\) right and left of the null position were available, the one with the best foveation during the calibration task was selected to be analysed, to allow for the maximum range of variation in foveation due to task conditions.

Due to the clear non-normality of the ordinal response variables (size and contrast), a fully nonparametric analysis by means of the rank-based ANOVA-type test for the within-subject observations (Brunner et al., 1999) was carried out using the statistical software environment R and the package nparLD (Noguchi et al., 2012). Here, simultaneous analysis of both response variables was accomplished through p-value Bonferroni adjustment. The factors load (low vs. high mental load) and gaze (at null vs. at away from null), as well as their possible interaction, were used as predictors.

5. Results

Table 1 shows clinical details for the participants included in the study, along with logMAR size and contrast level for the cutoffs at which subjects’ performance plateaued during the tasks with low and high mental load conditions. As explained above, ANOVA tests were restricted to eleven participants for whom measurements were possible for all task conditions and gaze positions with no missing data (8 male and 3 female; mean age ± SD: 31.0 ± 16.8 years).

For the performance measure “size”, which indicated the smallest optotype able to be identified by the subject, there was a significant interaction between the factors mental load and gaze position (nparLD package: \(T=6.0, p=0.028\)). The interaction is to be interpreted as follows. The elevation of thresholded target size from the low to the high mental load condition was more pronounced at the null position than at 15 degrees away from the null. At the null position, the relative treatment effect increased from 0.38 to 0.69 from low to high mental load conditions, respectively. At the away position, the increase was from 0.34 to 0.59. However, there was no significant interaction between these variables for the performance measure “lowest contrast achieved”. In addition, there was no significant effect of gaze position by itself on either of the task performance measures, size and contrast. Mental workload had pronounced effects on both
responses, with high mental load leading to significantly larger sizes (nparLD package: \( T=7.7, p=0.012 \)) and higher contrasts (nparLD package: \( T=12.6, p=0.00076 \)) being resolved.

No significant change was found between resting level and calibration for skin conductance level and heart rate, confirming that the calibration task elicited a low level of arousal or stress. We did not find any significant difference across tasks for skin conductance, possibly because it increases more under psychological stress, as induced by threat or motivation, rather than under cognitive loads such as mental arithmetic (Setz et al., 2010).

Two-way ANOVA for repeated measures tested significant effects of task and gaze position on percent change in pupil size from baseline. The results showed pupil dilation from baseline was significantly larger for the task with mental arithmetic than the task without mental arithmetic (0.2 ± 0.0%; \( f_{1,14}=5.015, p=0.001 \)). Change in pupil size from baseline was also by gaze position (\( f_{1,14}=10.517, p=0.006 \)), with no significant interaction with task.

One-way ANOVAs for repeated measures tested any significant effect of task on heart rate and MTE score. The results showed that task significantly affected MTE score (49.3±22.3; \( f_{2,16}=39.559, p<0.001 \)), and heart rate (6.1 ±5.1 bpm; \( f_{3,27}=12.203, p<0.001 \)). Post-hoc paired t-tests compared HR and MTE score between the tasks. The results showed a significant increase in HR during high mental load when compared to the low load (5.96±1.4 bpm, \( t_{12}=4.306, p=0.001 \)) and baseline (6.4±1.9 bpm; \( t_{10}=3.340, p=0.007 \)). Similar to heart rate, MTE score significantly increased during the high load when compared to the low load (28.8±8.3; \( t_8=3.466, p=0.008 \)) and baseline (69.7±8.1; \( t_8=8.553, p<0.001 \)). There was also a significant increase in MTE for the low load when compared to the baseline (40.8±7.1; \( t_8=5.759, p<0.001 \)). Figure 26 shows the subjective and physiological measures of mental workload across tasks.

Figure 27 shows the INS parameters for null and 15° away from it at baseline, under low mental load and high mental load during times of both low visual demand and high visual demand. Under high visual demand, a significant interaction between mental load (baseline, low and high) and gaze position (null and 15° away) was found for percent foveation time (\( f_{2,20}=4.651, p=0.02 \)). The interaction is to be interpreted as follows. The changes in foveation time from baseline due to changes in mental load were larger at the null position than at 15° away from it (14.19±0.74.6%; \( t_{21}=3.132, p=0.01 \)).

No other effects of visual demand or mental load approached significance.
Figure 26: Subjective MTE score and physiological measurements of mental workload including heart rate, mean skin conductance level and percent change in pupil size from baseline across tasks in INS subjects. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p < 0.0001.
Figure 27: Nystagmus parameters at baseline and under low and high mental load at null and 15° away from the null position, for high visual demand (a), and for low visual demand (b). Error bars indicate standard errors from the mean.
6. Discussion

Mental arithmetic demands active, ongoing behavior and therefore would appear to be an effective, consistent mental stressor (Recarte et al., 2008). Our subjective and physiological measurements of mental workload demonstrated that the level of mental load varied between our task conditions, and that a high mental load was induced during the acuity task with time restriction and mental arithmetic. The current study failed to find any significant main effects of the task on changes in the INS parameters, but addressed our hypothesis indicating that a task-induced change from baseline in INS parameters at the null position differs from task-induced changes at other gaze positions. Our results showed a significant interaction between mental load and gaze position on percent foveation time during high visual demand. Possibly, the sample size in the current study did not provide enough statistical power to show more statistically significant results, such as a main effect of the task on INS parameters. A further study with larger sample size could address this limitation. Another possibility might be that INS parameters are less sensitive to mental stress than are heart rate, pupil size, and visual task performance.

Cham et al. (2008b) and Jones et al. (2013) found that arousal and stress caused deterioration in the INS waveform; e.g., decreased foveation and increased frequency, amplitude, and intensity. These effects of stress on foveation were greater during tasks with high visual demand than during those requiring little effort to see. Tkalcevic and Abel (2005) and Cham et al. (2008b) did not find any changes in INS parameters due only to changes in visual demand. Our finding of no significant effect of visual demand on INS parameters agreed with Tkalcevic and Abel (2005), who suggested that changes in INS are affected by motivation; that is, the importance of the visual task to the individual, rather than solely being driven by the acuity level required to resolve the target details.

INS can be influenced by a range of internal states, such as the levels of motivation, attention, mental stress, and anxiety. While often noted anecdotally, these are often overlooked when assessing the vision of individuals with INS. No rewards or performance feedback were provided in our experiment, and thus the importance of the visual task to the participant and the subsequent visual effort exerted was probably not large enough to have a significant effect on the waveform parameters (Tkalcevic & Abel, 2005). In contrast to the preceding studies, Wiggins et al. (2007) reported that INS improved (that is, had longer foveation with less intensity) when
participants with INS responded to smaller, harder to identify targets at their null position and did so in the absence of any concurrent secondary task, either stressful or motivating. Wiggins et al. (2007) discussed the differences between attempting only to resolve target details and doing so in the presence of concurrent tasks with mental load or stressors. They suggested that these evoked different responses, and should be considered independently. While “effort to see” includes subjects’ concerted effort to resolve target details, the visual task could incorporate stress and/or arousal (Wiggins et al., 2007). The value of having a concurrent mental task to manipulate stress levels is that it separates this internal state from those directly related to visual performance. A comparison of high versus low visual demand in the present study showed no significant effect on INS parameters. Neither the current study nor the study by Cham et al. (2008b) were designed to measure visual acuity, considered as the minimum angle of resolution at 100 % contrast, due to limitations in the display. However, this limitation was much greater in the current study than the study by Cham et al. (2008b) with stimulus size ranged -0.1 to 1.2 logMAR with 0.1 logMAR step, as their use of a single gaze position allowed the use of an LCD monitor instead of a projector.

One limitation of our study is that we did not measure contrast sensitivity or visual acuity. Presenting small sized targets was not possible with a 1024 x 768 pixel resolution projector, which was the highest resolution available at the time the study commenced. Therefore, in order to be able to decrease the visibility of the targets when we could no longer reduce their size, we compensated by decreasing the contrast to increase visual demand. Although our method looks similar to low contrast sensitivity acuity tests such as Sloan, we were unable to present small optotype sizes. While decreasing both size and contrast made a target harder to resolve, it is not clear if small targets at 100% contrast would produce the same effects on INS as larger, low contrast targets. Disambiguating this will require further studies using higher resolution displays.

Jones et al. (2013) suggested that both foveation duration and frequency contribute to visual function in INS. According to them, shorter foveation duration together with increased frequency could protect visual acuity through temporal summation of consecutive foveation periods, thus increasing total exposure time. We aimed to vary effort to see by manipulating the contrast and size of the targets. Although our experiment was not designed to measure either contrast sensitivity or visual acuity, we observed that the high mental load condition degraded task performance, especially at the null. Our findings for task performance agreed with a previous
study that found task performance in INS patients decreased at all gaze positions when target viewing was time restricted; this experiment was done without a secondary mental task (Yang et al., 2005). However, Jones et al. (2013) reported longer recognition times, but slightly better visual acuity with stress within a group of individuals with INS. Time of target presentation was not limited in their study. They proposed an increase in total exposure time under these conditions through the use of shorter but more frequent foveation periods. They suggested that visual acuity can change, irrespective of the changes in foveation, because patients with INS may use this total exposure time to identify the visual targets, rather than depending upon the duration of individual foveation periods. While 0.7-1 sec has been reported to be required for decision making in normal participants under stress (Jones et al., 2013), visual targets were presented only for 0.5sec in our high mental load condition, which could have resulted in deterioration of visual performance due to insufficient exposure time.

Our data demonstrates, for the first time, the effects of changes in internal state on INS parameters differed at null from at a gaze position away from the null. Our target presentation time differed between tasks and between subjects during the low mental load trials. Thus, we did not measure total exposure time. No study has yet measured the effects of mental load and visual demand on the total exposure time within a restricted time. We found that task-induced changes in foveation from baseline varied between gaze positions. Since the sum of individual foveation periods contributes to total exposure time (Jones et al., 2013), it seems that the effects of task on changes in total exposure time from baseline could therefore vary with gaze position. While Jones et al. (2013) suggested that total exposure time affects visual task performance in INS, our results suggest that the effects of task on performance may be larger at null for the following reasons: first, foveation is more likely to change from baseline; second, an increase in INS frequency is unlikely to raise the total exposure time enough to improve performance on visual tasks unless the viewing time is long enough to do so.

Outcomes of nystagmus treatments have been evaluated within subjects at various gaze angles both directly by a using logMAR scale and visual acuity chart (Hertle & Yang, 2006) or indirectly by calculating indices such as using the expanded nystagmus acuity function (NAFX) (Wang, Dell’Osso, Jacobs, et al., 2006; Wang et al., 2007; Taibbi et al., 2008), a formula that has been developed to predict best potential visual acuity based on eye movement data, but that does not directly measure visual acuity (Dell’Osso & Jacobs, 2002). This latter approach involves
using an index developed across a patient population to predict visual outcomes in an individual, and this may be problematic. The relationship between visual acuity and INS parameters has been found to be inconsistent. Bedell and Loshin (1991) found no significant correlation between INS parameters and visual acuity, measured both with Landolt Cs and gratings, within a group of subjects. Dunn et al. (2014) found eliminating retinal image motion in patients with INS does not necessarily increase their grating visual acuity. They argued that predicted visual acuity based on eye movements cannot reliably predict actual perceptual treatment outcomes in individual patients with INS, especially given that the expanded nystagmus acuity function (NAFX) has been developed based on data from a large group of subjects rather than using changes within subjects. Significant inter-subject correlation has been found between visual acuity and foveation when measured as is commonly done clinically; that is by means of clinical acuity charts, and foveation duration calculated from eye movement recordings while patients with INS view simple fixation targets such as LEDs (Abadi & Worfolk, 1989; Guo et al., 1990; Dell'Osso & Jacobs, 2002). Although visual acuity was not measured in the current study, our results showed that a change in both visual performance and foveation due to task changes was larger at the null than away from it. We found maximum foveation during the baseline calibration task at the null, when no discrimination or recognition of a visual stimulus was required. Whereas the NAFX is calculated using foveation measures obtained during the viewing of such simple targets, it is possible that such prediction of visual acuity may overestimate or underestimate acuity if internal state and visual demand change, as would often be the case in daily life.

Even if individual foveation periods become shorter, there may still be a longer total exposure time through an increase in nystagmus frequency arising from possible changes in individuals’ internal state. In addition to task demands that may affect foveation, viewing time should also be considered when evaluating how vision might vary during the performance of daily tasks by individuals with INS (Jones et al., 2013). The possibility of INS parameters varying with increased time on task is unknown and has not been addressed in the current study. This is entirely different from individuals with normal ocular health conditions, whose eyes are not oscillating and whose acuity is very unlikely to vary significantly with changes in task such as limited viewing time or being placed under stress (Yang et al., 2005; Jones et al., 2013). Thus, both viewing time and accuracy of the responses to the visual targets need to be considered when measuring visual performance in patients with INS (ElKamshoushy et al., 2012).
7. Conclusion

Our experiment suggests that the extent to which foveation duration contributes to visual performance can vary across both task conditions and gaze positions. We believe the nature of the task being carried out should be considered when visual performance is evaluated in individuals with INS. Estimates of visual acuity based on eye movement recording during the viewing of a simple, low visually demanding target, may result in visual performance being overestimated beyond what a patient might experience under conditions arising in daily life (Sheth, Dell'Oso, Leigh, Van Doren & Peckman, 1995; Abadi & Bjerre, 2002; Hertle et al., 2002; Yang et al., 2005).
Chapter five: Saccade experiment in the INS group

1. Background and Aims

Usual visual acuity tests such as the Snellen chart do not represent every aspect of visual function in the real world (Kutzbach et al., 2009), especially in patients with INS (Sprunger et al., 1997). Many patients with INS describe an enhancement in their visual function post-INS therapy that could not be identified by visual acuity tests (Sprunger et al., 1997; ElKamshoushy et al., 2012). Comparing a group of participants with INS with a normal control group has shown that individuals with INS are slower in responding to acuity targets than normal individuals (Hertle et al., 2002; Jones et al., 2013). Measuring the speed of performance in visual tasks has been considered as a useful indicator of visual function impairment resulting from INS (Sprunger et al., 1997; Hertle et al., 2002; Wang & Dell'Osso, 2007a; Jones et al., 2013). Sprunger et al. (1997) showed that nystagmus surgery decreased the time needed to recognise visual targets which were presented at a fixed gaze position. To respond to an object of interest under real world conditions, a complex mixture of visual tasks may be required; this can include target acquisition, visual sampling during target inspection time, processing of collected information, and making a decision to respond. These steps have no clear time boundary between them (Recarte & Nunes, 2003).

Patients with INS take more time to foveate on visual targets, suggesting that longer target acquisition time contributes to the phenomenon of “slow to see” (Wang & Dell’Osso, 2007a; Dunn et al., 2015), an impression of recognising visual objects late among the patients with INS (Sprunger et al., 1997). Wang and Dell’Osso (2008) have suggested that a decrease in target acquisition time through changes in foveation can make an improvement in being slow to see. Furthermore, Dunn et al. (2015) found that once a visual stimulus was fixated, patients with INS took a similar time to process visual stimuli when compared to normal subjects. Hence, they have suggested that visual processing time, defined as the period from initial target acquisition until a response to the same target is made, is normal in INS (Dunn et al., 2015).
Under real world conditions, both refixation and visual processing may be required in the presence of a high mental load. A high cognitive load induced by a concurrent mental task can increase saccade latency and subjects’ response time to visual objects in normal individuals (Stuyven et al., 2000; Halliday & Carpenter, 2010). As explained in the previous chapter, it has also been suggested that patients with INS can resolve target details via temporal summation of repeated foveation periods during target viewing (Jones et al., 2013). Meanwhile, task demands and internal states such as stress, motivation, and arousal have been found to have an effect on INS parameters, including foveation time and INS frequency (Abadi & Bjerre, 2002; Wiggins et al., 2007; Cham et al., 2008b; Jones et al., 2013). While surgical treatments of INS can have an effect on target acquisition time and subjects’ reaction time when responding to a visual target (Sprunger et al., 1997; Wang & Dell’Osso, 2008), changes in INS arising from variations in task conditions may also affect target acquisition time and visual processing time. However, eye movement analysis has yet to be carried out to measure target acquisition time and visual processing time across task conditions in patients with INS.

Here, we aim to explore two points. The first is to address whether or not a high mental load results in a greater impairment of visual task performance compared to a low mental load in individuals with INS, than is the case in normal controls. Like the saccade experiment described in chapter 3, visual task performance is defined as response accuracy and response time when identifying the direction of an ‘E’ target. The second point tests the possibility that slowness in target acquisition and visual processing due to the high mental load contributes to poor task performance in patients with INS when compared to normal controls. To address these points, we have recorded eye movements and visual task performance in a group of normal controls and a group of patients with INS during a saccade task, under a low mental load and a high mental load condition. Our experimental protocol allows us to investigate the separate components (target acquisition and processing times) which may contribute to the phenomenon of being slow to see described by the individuals with INS, and doing so under a mental stress condition bearing a closer resemblance to what may be encountered in daily life. The results will aid better evaluation of visual function in INS, especially in terms of more fully assessing the outcomes of INS therapies.
2. Method

2.1. Participants

The same participants with INS who took part in the acuity experiment, discussed in the previous chapter, participated in the current experiment as the nystagmus group. Thus, this group was comprised of fifteen adult participants with INS (6 female and 9 male; mean age ± SD: 28.4 ± 15.5 years), none of whom had fusion maldevelopment nystagmus syndrome or congenital periodic alternating nystagmus. Twenty-five volunteers who participated in the experiments explained in chapter 3, also took part in this experiment as a control group (10 female and 15 male). These participants were age-matched with the participants with INS and had saccade data available for target positions ≥15° away from the centre, as used in the current experiment.

Table 2 explains the clinical details of participants with INS. All participants in the INS group were required to wear their habitual optical correction, if they had any, during the tasks. Section 2.1 in Chapter 3 and section 2.2 in Chapter 4 explained the characteristics of participants in the control group and INS group respectively in more detail.

2.2. Procedures

The experimental procedure was similar to the procedure used for the saccade experiment in normal individuals described in chapter 3, and consisted of four parts in this order: calibration of the eye tracker, a baseline task (calibration run), and tasks specified for the saccade experiment that imposed a low and a high level of mental load. Below, each part of the experimental procedure has been explained, highlighting any modifications and differences, with the saccade experiment explained previously for normal participants in chapter 3, section 2.2.

2.2.1. EyeLink II calibration

As explained in chapter 3, we carried out separate eye tracker calibration runs for the saccade experiment and acuity experiment in normal participants. Similar to the normal group, a separate
Table 2: Characteristics of individuals with idiopathic INS who participated in the study.

<table>
<thead>
<tr>
<th>Part.</th>
<th>Null position</th>
<th>Waveform</th>
<th>Habitual correction</th>
<th>Eye tested</th>
<th>Visual acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-20°</td>
<td>Jef</td>
<td>R:-3.00/-3.75×165° L:-3.25/-3.50×25°</td>
<td>R</td>
<td>R: 6/7.5 L: 6/7.5</td>
</tr>
<tr>
<td>4</td>
<td>+5°</td>
<td>P, DJR, PCL</td>
<td>R:+4.00/-0.50×140° L:+4.25/-2.25×143°</td>
<td>L</td>
<td>R: 6/24 L: 6/24</td>
</tr>
<tr>
<td>5</td>
<td>+5°</td>
<td>Pfs, PC</td>
<td>R: Plano L: Plano</td>
<td>R</td>
<td>R: 6/18 L: 6/18</td>
</tr>
<tr>
<td>6</td>
<td>0°</td>
<td>Jef</td>
<td>R:+5.00/-5.00×180° L:+4.00/-4.00×180°</td>
<td>L</td>
<td>R: 6/15 L: 6/12</td>
</tr>
<tr>
<td>7</td>
<td>-20°</td>
<td>Jrf</td>
<td>R:+0.50 sph L:+0.75 sph</td>
<td>L</td>
<td>R: 6/7.5 L: 6/7.5</td>
</tr>
<tr>
<td>8</td>
<td>-20°</td>
<td>JLf</td>
<td>R:-1.50/-1.25×5° L:-0.75/-1.25×175°</td>
<td>R</td>
<td>R: 6/7.5 L: 6/7.5</td>
</tr>
<tr>
<td>9</td>
<td>+20°</td>
<td>BDJ, AP</td>
<td>R:-1.00/-2.00×145° L:0.25/-2.00×05°</td>
<td>R</td>
<td>R: 6/24 L: 6/24</td>
</tr>
<tr>
<td>10</td>
<td>+10°</td>
<td>DJL, AP, PCL</td>
<td>R: Plano L:Plano</td>
<td>L</td>
<td>6/12 6/12</td>
</tr>
<tr>
<td>11*</td>
<td>0°</td>
<td>PPfs</td>
<td>R: Plano L: Plano</td>
<td>R</td>
<td>R: 6/9 L: Lp</td>
</tr>
<tr>
<td>12</td>
<td>&gt;+25°</td>
<td>DJ</td>
<td>R:+6.75/-1.00×180° L:+6.00 sph</td>
<td>L</td>
<td>R: 6/24 L: 6/15</td>
</tr>
<tr>
<td>13</td>
<td>-25°</td>
<td>JR</td>
<td>R:-2.75 sph L:1.50 sph</td>
<td>R</td>
<td>R:6/9 L:6/12</td>
</tr>
<tr>
<td>14</td>
<td>&gt;+25°</td>
<td>JLf</td>
<td>R:-0.50/-1.00×90° L:-0.50/-1.00×88°</td>
<td>R</td>
<td>R: 6/24 L: 6/24</td>
</tr>
<tr>
<td>15</td>
<td>-5°</td>
<td>DJR, Pfs</td>
<td>R:-0.50/-3.25×90° L:-1.50/-2.00×90°</td>
<td>L</td>
<td>R:6/48 L:6/48</td>
</tr>
</tbody>
</table>

All measurements and eye movement recording were done with the participants’ habitual correction. Part., Participants’ code; Eye tested refers to the eye which was selected for analysis in the current study. R and L refer to right and left eyes; LP., light perception only; Nystagmus waveforms are: jerk (J), dual jerk (DJ), pseudocycloid (PC), jerk with extended foveation (Jef), Pendular with foveating saccades (Pfs), Bidirectional jerk (BDJ), Asymmetric pendular (AP), and pseudopendular with foveating saccades (PPfs).; \*: Participant has retinal arterial occlusion in the left eye which was persisted for a long time.
EyeLink II calibration was required before data collection for the saccade experiment in the INS group. Chapter 3, section 2.2.1 provided details of EyeLink II calibration in the normal group. Details of EyeLink II calibration for the saccade experiment in the INS group is also the same as explained for the acuity experiment (see chapter 4, section 2.3.1).

2.2.2. **Baseline task (calibration run)**

The baseline task is similar to that described previously for normal participants and participants with INS (see chapter 3, section 2.2.2. for controls, and chapter 4, section 2.3.2 for the INS group). As explained before in chapters 3 and 4, we used the baseline task to convert the scale of the horizontal eye positions from pixels to degrees. The selection of the eye for data analyses was as explained in chapter 4 (see Table 2).

2.2.3. **Saccade experiment**

The saccade experiment consisted of two main post-saccadic discrimination tasks that contributed to induce low and high levels of mental stress. The method for the saccade tasks was similar to the method used in the experiments in normal participants (chapter 3, section 2.2.3), with two important differences concerning the INS group. Before the tasks started, the examiner ensured that the size of the horizontal tumbling E target was above the acuity threshold for each individual with INS across all gaze positions. That was achieved by presenting a screen which consisted of horizontal tumbling E targets across ± 25° horizontally away from the centre with 5° steps, before the saccade tasks started. The examiner asked each participant with INS whether the details of the targets (directed randomly to right or left) were visible across all gaze positions. The examiner increased the size of E targets if the participant had trouble correctly reporting the direction of a target presented at any of the gaze positions; for example, if a head turn was required to resolve target details.

After the size of the target was determined for each participant with INS, the examiner presented the saccade tasks – those included both target trials and return trials. As explained in chapter 3-section 2.2.3, a central fixation point was presented during return trials of the saccade
tasks when participants were required to look back to the centre, and wait for another target trial to be presented randomly. For each participant, the size of the central fixation point was the same as the size of horizontal tumbling E targets. Each target trial presented a horizontal tumbling E target in an eccentric position randomly across ± 25° horizontally away from the centre with 5° steps. Similar to the saccade experiment in normal controls (see chapter 3-section 2.2.3 for details), participants were required to perform a post-saccadic discrimination task under two conditions that induced low and high levels of mental load. For high mental load, there was an important difference in the time limitation between groups. Time limitation increased from 1.00 second in normal controls to 1.50 sec in the INS group. Although all participants were aware that the response time was limited under high mental load, they were not aware of its exact duration. Section 2.2.3 of chapter 3 explains the saccade experiment in more details.

Again, we confirmed the induced level of mental load, low or high, using the change in heart rate from that obtained during the baseline task. Similar to chapters 3 and 4, the MTE score of NASA-TLX was used as the measurement of subjective mental workload.

2.3. Apparatus

The apparatus used to present stimuli, record eye movements and heart rate were the same as used in previous experiments in chapter 3 with normal participants, and in chapter 4 for participants with INS. The details of the apparatus are identical with those explained in section 2.3 of chapter 3.

3. Data preparation

The method to measure heart rate across task conditions was the same as before (see section 3.1.1 of chapter 3).

All digital data collected for horizontal eye position data were filtered as explained in chapter 3, section 2.3. Eye velocity and acceleration were calculated offline. Separate custom written programs in MATLAB R2012a were used for controls and the INS group to analyse filtered eye position data. The program used to analyse data in the control group was the one explained
previously for the saccade experiment in normal participants (see chapter 3, section 3.3.1). Both programs identified the potential saccades for all participants with the criteria of 8000°/sec² acceleration and 10°/sec velocity for saccade onset and offset after each target step. The investigator reviewed all potential saccades manually before selection for subsequent analysis. Target acquisition time in the control group was defined as the time taken to fixate on the E target with an accuracy of ±0.5°. Saccades with a gain of less than 0.5 or greater than 1.5 in the control group were excluded from data analyses (Bieg et al., 2012). The program used for the INS group has been described in more detail below.

The examiner reviewed all potential saccades determined by the MATLAB program in INS group before selection for analysis. This was to make sure that the program detected the right time point as the beginning of saccade in INS. The beginning of a saccade was defined as the direction-changing point of the velocity trace in the INS waveform (Wang & Dell'Osso, 2007a). The investigator could manually select a data point that looked to be the beginning of the saccade, if required. Also, the examiner manually determined the time points of the beginning and end of the INS cycle. The time between the beginning of the INS cycle and target onset, within the same cycle, provided normalised stimulus time within the cycle (Tc%) after it was divided by duration of the cycle (Wang & Dell'Osso, 2007a). Foveation window was determined by criteria of 4°/sec for eye-velocity and ±0.5° away from the desired target for eye position. To determine a foveation, at least 4 consecutive samples (8 msec) were required to be within the foveation window. This period is similar to the duration criterion used by Dell'Osso and Jacobs (2002) to determine a valid foveation time of 7 msec.

Target acquisition time was measured from target onset time at a new position until the desired target was initially acquired; that was when the eye position was located for the first time inside the foveation window. Additional INS cycles may have followed initial target acquisition until the participant could extend foveation time duration and maintain a similar eye position for foveation (Wang & Dell'Osso, 2007a). Figure 28 represents the data of interest in a trial during which a participant with INS used a prosaccade for target acquisition. For each participant with INS, the trial was marked if no reflexive prosaccade was used to get on the target.
Figure 28: A participant with a jerk with extended foveation INS waveform used a reflexive saccade to get on the target. The reflexive saccade has been marked by a custom written program MATLAB in green. Dashed line “a” represents the start of the INS cycle. Dashed line “b” represents presentation of the E target on the screen. Dashed line “c” shows the end of the INS cycle and the start of the reflexive saccade. Dashed line “d” shows the end of the reflexive saccade. Dashed line “e” shows where initial target acquisition has occurred.

The trials with small target steps (5-10°) were not included in the analysis. The trials associated with inattention, blinks, and predictive eye movements or with directional errors were also excluded from the study.

For both controls and the INS group, response time (reaction time) was measured from when the E target was presented on the projector screen (as indicated by a photocell installed at the corner of the screen) until a response was submitted by the participant. Response errors were recorded for each participant as incorrect or lapsed (>2sec) responses in the discrimination task. Visual processing time was measured as the time between initial target acquisition and participants’ response to the post-saccade target. For the INS group, total exposure time was measured for all task conditions, which was defined as the sum of foveation time durations during the processing period. The position criterion for the foveation window was raised to ±1.0° when measuring exposure time. For each individual participant in the INS group, the positions of post-saccade targets were the same between tasks.
4. **Statistical tests**

Using IBM SPSS Version 20, an ANOVA for repeated measures was used to investigate any effect of group and task (low and high mental load) for heart rate, reaction time, saccade latency, target acquisition time, and processing time. Normality of the data distributions was investigated using the Kolmogorov-Simonov test. In cases where sphericity could not be assumed, Greenhouse-Geisser corrections were used. Bonferroni correction for multiple comparisons was used to adjust p-values. Low and high mental loads were investigated with a paired t-test for any significant difference in total exposure times.

Similar to the previous chapter’s analysis of task performance, a fully nonparametric analysis by means of the rank-based ANOVA-type test was carried out using the statistical software environment R and the package nparLD (Brunner et al., 1999; Noguchi et al., 2012). The factors load (low mental load vs. high mental load) and group (controls vs. INS group), as well as their possible interaction effect, were used as predictors. P-values were adjusted through Bonferroni correction.

Using between-subjects data in each group, we conducted Spearman correlations to test for any significant associations between changes in task performance (*response accuracy in the discrimination task*) due to mental load with any changes in eye movement measurements. Using GraphPad Prism Version 5 for Windows, eye movement variables saccade latency, target acquisition time, visual processing time, and exposure time were used as predictors of task performance, i.e., response accuracy. Tc% was plotted versus target acquisition time both within subjects and separately for each INS waveform. Any relationship between target acquisition time and Tc% was investigated by attempting to fit a polynomial curve or straight line through the data points.

5. **Results**

Repeated measures ANOVA was used to test for any significant effect of group and task on heart rate and MTE scores. The results showed a significant effect of task on heart rate and MTE
score within subjects; i.e. heart rate and MTE score increased during the task with time restriction and concurrent mental arithmetic when compared to the task without time restriction and mental arithmetic (for HR: mean±SEM: 9.6±0.93 bpm; 95% CI: 7.7, 11.5; \( f_{1,35}=105.25, p<0.001 \); for MTE score: 39.58±3.53; 32.35, 46.81; \( f_{1,29}=125.35, p<0.001 \); figure 28).

There was no significant effect of group on heart rate or MTE score. Hence, we concluded that mental load differed between the tasks and that the task with mental arithmetic and time restriction induced high mental load within subjects in both groups.

![Graph showing change in heart rate and subjective MTE score](image)

**Figure 29:** Change in heart rate from baseline (a), and subjective MTE score (b) in saccade tasks with low and high mental load. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***\( p < 0.0001 \).

Figure 30 shows samples of the common strategies, except for a single reflexive saccade, used by our INS participants for target acquisition. Attempts to fit a linear or polynomial line to plots of target acquisition time versus Tc% for individual subjects, and for pooled data for similar INS waveforms, showed low values for \( R^2 \) (<0.1) and probability of line deviation from zero, with no significant difference between slopes of lines fitted for low and high mental load (p>0.05). Figure 31 shows data for jerk and pendular with foveating saccades waveforms across tasks.
Figure 30: Samples of strategies used by participants with INS for target acquisition. For each sample, blue trace represents horizontal eye position and green trace represents eye velocity. (a): a participant used a mixture of slow eye movements and a reflexive saccade towards target position. The reflexive saccade directed towards target position has been marked in green by a custom written MATLAB program. Arrows “a” and “b” indicate the start and end of the saccade respectively. The black arrow indicates target acquisition. (b): a participant used a slow eye movement for target acquisition. The arrow indicates target acquisition. (c): a participant made an eye movement in the wrong direction followed by a large saccade towards the correct target position. This trial was excluded from data analyses due to the possibility of predictive eye movement.
Figure 31: Normalised time of stimuli within cycle (Tc%) versus target acquisition time for (a): participants with jerk INS waveform, and (b): participants with pendular INS waveform with foveating saccades.
Repeated measures ANOVA was used to test for any significant effect of group and mental load on the variations, measured as standard deviations of the saccade task variables; i.e. saccade latency, target acquisition time, saccade gain, and subjects’ reaction time (see table 3 for the statistical results). Standard deviations of the saccade task variables were significantly larger under high mental load when compared to the low mental load, and except for saccade latency, was also larger in the INS group when compared to the controls (figure 32).

The interaction between mental load and group significantly affected only the variations of subjects’ reaction time \( (115.05 ± 2.13 \text{ ms}; 119.3, 110.73; f_{1,37}=16.95, p<0.001) \), i.e. the mean SD of subjects’ reaction time decreased with high load in the control group but increased with high load in the INS group. A paired t-test showed the variations in visual processing time within INS subjects significantly increased from low to high mental load \( (63.38 ± 26.64 \text{ ms}; 120.92, 5.83; t_{13}=2.379, p=0.033) \).

### Table 3: Results obtained from repeated measures ANOVA testing the effects of subjects’ group and mental load level on standard deviations of saccade latency, target acquisition time, saccade gain and reaction time.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Within subjects comparisons (mean change ±SEM from low to high load; 95% CI)</th>
<th>Between groups comparisons (mean change ±SEM in INS group from control group; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (sec)</td>
<td>( f_{1,1}=34.83, p&lt;0.001 ) ( (0.037 ± 0.004; 0.035, 0.006) )</td>
<td>( f_{1,38}=0.574, p&gt;0.45 ) ( (0.010±0.007; 0.010,0.009) )</td>
</tr>
<tr>
<td>Target acquisition time (sec)</td>
<td>( f_{1,38}=10.87, p=0.002 ) ( (0.028 ± 0.009; 0.011, 0.046) )</td>
<td>( f_{1,38}=20.34, p&lt;0.001 ) ( (0.42 ± 0.009; 0.061, 0.023) )</td>
</tr>
<tr>
<td>Saccade gain</td>
<td>( f_{1,38}=5.07, p=0.03 ) ( (0.021 ± 0.009; 0.002, 0.039) )</td>
<td>( f_{1,38}=106.014, p&lt;0.001 ) ( (0.021 ± 0.02; 0.25, 017) )</td>
</tr>
<tr>
<td>Reaction time (sec)</td>
<td>( f_{1,37}=4.72, p=0.036 ) ( (0.030±0.014; 2.04, 58.66) )</td>
<td>( f_{1,37}=634.45, p&lt;0.001 ) ( (0.087 ± 0.014; 58.71, 114.70) )</td>
</tr>
</tbody>
</table>

*Significant p-value with \( \alpha<0.05 \)
Figure 32: Variations in saccade latency (a), target acquisition time (b), saccade gain (c) and subjects’ reaction time (d) under low and high mental loads for control and INS subjects. Black lines represent changes in standard deviations (SDs) from low to high mental load. For each group, red circles with vertical lines express the mean ± SEM of the SDs under low and high loads. Change in the mean of the SDs from low to high mental load is represented for each control and INS subjects by a red diagonal line. Pairwise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p<0.0001; **0.001<p<0.01; *0.01<p<0.05.

The percentage of the trials with reflexive prosaccades towards the target was 73.3% for the low mental load and 66.7% for the high mental load for INS subjects, with no significant difference between the tasks (paired t-test: p>0.05). ANOVA was used to test for any significant effect of group and task on the mean gain of reflexive saccades within subjects. The results yielded a significant interaction between task and group for the gain of reflexive saccades (0.16 ± 0.004; 0.15, 0.17; f1,38=8.64, p=0.006). Unlike controls, for whom the mean of saccade gain appeared to increase under high mental load (see also section 5.3.1.1 in chapter 3), mean saccade gain appeared to decrease under high mental load in the INS group (Figure 33 a).
Figure 33: Eye movement indices of target acquisition in control and INS groups including means of saccade gain (a), saccade latency (b), target acquisition time (c) and visual processing time (d) under low and high mental load conditions. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA. ***p < 0.0001.

The correlation between the changes in saccade gain and the changes in heart rate or target acquisition time from low to high mental load was not significant (p>0.1).
Similar to the saccade gain, explained above, the effect of task and group on means of saccade latency, target acquisition time, visual processing time and subjects’ reaction time were tested using repeated measures ANOVAs. The results were as below.

Both means of latency of saccades (Ls) and target acquisition time (Lt) significantly increased in the INS group compared to the control group (for Ls: 39.79 ± 7.80 ms; 23.98, 55.62; \( f_{1,36}=26.027, p<0.001 \), for Lt: 134 ± 19 ms; 96, 172; \( f_{1,38}=50.955, p<0.001 \)).

Also, both saccade latency and target acquisition time increased for the high mental load task when compared to the low mental load task (for Ls: 32.69 ± 5.68 ms; 21.17, 44.20; \( f_{1,36}=33.138, p<0.001 \); for Lt: 57 ± 12 ms; 81, 34; \( f_{1,38}=23.876, p<0.001 \)).

The interaction between task and group was not significant for Ls (figure 33 b); however, it was significant for Lt (37.93± 0.51 ms; 36.91, 38.96; \( f_{1,38}=7.161, p=0.011 \); Figure 33 c; the trials with missing data for the subjects’ response to the post-saccadic target were excluded).

Mean of visual processing time was not significantly affected by task or group (p>0.2). Normal controls appeared to show shorter visual processing time with high mental load than with low mental load (figure 33 d), but the interaction between task and group fell short of significance (98.19 ± -2.17 ms; 102.60, 93.79; p=0.08). Subjects’ reaction time was longer in the INS group than the control group (135.43 ± 43.03 ms; 48.32, 222.55; \( f_{1,38}=9.905, p=0.003 \)). The interaction between task and group was significant for reaction time, which increased in the INS group when compared to the controls under high mental load (95.37 ± 14.55 ms; 124.84, 65.91; \( f_{1,14}=4.975, p=0.043 \), Figure 34 a).

Exposure times measured in INS did not change significantly with the high load than with the low load (-8.09 ± 9.10 ms; -27.92, 11.74; paired t-test: p=0.39).

Using nparLD package, explained in section 4.2.1 of chapter 1, the effects of task and group were tested on subjects’ reaction time and response errors. The results were as follow. Across both groups, there were larger percentages of response errors for the high mental load (p< 0.001, Figure 33 b). This was also the case when considering both groups separately: for each group individually, higher mental load led to larger percentages of response errors (p< 0.001 in each case). There were also slightly larger percentages of response errors for INS than controls, but
these were not statistically significant (p=0.085 before adjustment for multiple testing; p>0.2 after adjustment). No indication of an interaction was found between the mental load and group for task performance (p=0.57).

Figure 34: Task performance indices for the post-saccade discrimination task under low and high mental loads for control and INS groups, including (a): subjects’ reaction time, with error bars indicating standard errors from mean, and (b): percentage of response errors; i.e., missed and inaccurate responses to E targets, with lines indicating median and interquartile range. Pair wise comparisons were conducted using post-hoc analyses of repeated measures ANOVA for subjects’ reaction time, and using non-parametric repeated measures test (nparLD) for response errors. ***p < 0.0001; **0.001<p< 0.01.

For normal controls, an increase in response errors was correlated with a decrement in visual processing time (r= -0.484, p=0.014; Figure 35 a), and subjects’ reaction time (r= -0.492, p= 0.013; figure 35 b). For the INS group, no significant relationship was found between response accuracy and saccade latency, target acquisition time, subjects’ reaction time, visual processing time, or total exposure time.
Figure 35: Scatter plot of changes in response errors versus changes in visual processing time (a) and subjects’ reaction time (b) due to the increase in mental load. Each point represents a subject. The linear regression line is shown by the solid line, with the dashed lines representing 95% confidence intervals from the mean. The plot is of the control group data.
6. Discussion

Saccade latency can indicate the extent to which various factors have an effect on the process of decision making (Halliday & Carpenter, 2010). The neural network that is required to support mathematical thinking requires widespread activations in various parts of the brain that also play a key role in eye movements, including frontoparietal connections (Dehaene & Cohen, 1995; Corbetta & Shulman, 2002; Hubbard et al., 2005; Kong et al., 2005; Knops et al., 2009; Klein et al., 2013). Measuring cardiovascular changes is a well-established technique to monitor the level of stress elicited by mental arithmetic (Zygmunst & Stanczyk, 2010). Our finding that high mental load, evidenced by increased heart rate and a retrospective subjective mental workload measurement, increased saccade latency agrees with the fact that eye movements share similar neural mechanisms with attention shifts (Kustov & Robinson, 1996; Simon et al., 2002). For both controls and INS groups, we found that the variability of saccade measurements increased under high mental load when compared to low mental load. The possible reason for this finding might be saccades are sensitive to small variations in cognitive processes and mental workload. The variability of the saccade measurements were larger during the task with mental arithmetic, possibly due to the attentional resources allocated to the saccade task varying with mental arithmetic. Eye movements have been found to be susceptible to attentional disruption and interference by a secondary cognitive task, such as the arithmetic task used in this study; these changes in eye movements can manifest in several ways, one of which being delayed execution of prosaccades (Pashler et al., 1993; Roberts et al., 1994; Hoffman & Subramaniam, 1995; Kowler et al., 1995; Deubel & Schneider, 1996; Duncan et al., 1997; Stuyven et al., 2000; Kane et al., 2001; Kristjánsson et al., 2001; Montagnini & Chelazzi, 2005; Irving et al., 2009; Drewes & VanRullen, 2010; Guyader et al., 2010; Drewes & VanRullen, 2011).

Recarte and Nunes (2003) measured subjects’ reaction time and target acquisition time during a visual search task without and with a high mental load induced by a concurrent visual discrimination task. Similar to our results for controls, Recarte and Nunes (2003) found that high mental load resulted in increased target acquisition time while subjects’ reaction time remained unchanged, indicating a trend towards a decrement in visual processing time through various strategies such as blink inhibition. The results of our study agreed with this. We also found a
speed-accuracy trade-off in the control group, indicating that more response errors were associated with shorter visual processing time due to mental load. Our results agreed with Recarte and Nunes (2003) who suggested that visual performance can be impaired in the presence of endogenous distracters produced by internal states such as concurrent irrelevant cognitive activity, and that this decline in performance is due to poor visual processing per se, rather than to a shortage of visual processing time. In other words, mental disruption by a concurrent cognitive task can make subjects less attentive to the visual task resulting in more response errors even with no statistically significant change in visual processing time.

Unlike for normal individuals, stable visual sampling in INS is limited to sequences of foveation times (Jones et al., 2013). However, processing of the information gathered can occur during the entire INS cycle (Dell'Osso, 2014; Dunn et al., 2015). Dunn et al. (2015) suggested that visual processing time after foveation is made is normal in INS. We did not find any statistically significant effect of group (main effect or interaction with the task) on the mean visual processing time. Our results agreed with Dunn et al. (2015), indicating that visual processing time is statistically similar between INS and normal individuals, even in presence of mental load as shown in the current study. However, unlike the case for normal controls, visual processing time in the INS group did not tend to decrease with high mental load (see figure 33d). Probably, the larger variations of visual processing time found with the high load in INS group than controls contributed to the reaction time varying more from low to high mental load within INS subjects, as opposed to the controls. Under low visual demand, we found that the effects of mental load on the accuracy of a visual task were similar between INS and normal groups, but the speed of performing the visual task decreased from low to high mental load in the INS group when compared to controls. Target acquisition time and the subsequent viewing time required to collect and process visual information contribute to slowness of visual recognition in INS (Wang & Dell’Osso, 2008; Jones et al., 2013). Stress has been reported to increase both INS subjects’ reaction time and nystagmus frequency, and also to decrease foveation time (Cham et al., 2008b; Jones et al., 2013). Foveation time has been found to contribute to target acquisition time (Wang & Dell’Osso, 2008) and total exposure time (Jones et al. 2013). Jones et al. (2013) suggested that total exposure time affected the resolution of target details in INS, and can be increased through lengthening of target viewing time when INS deteriorates; i.e., when foveation time becomes shorter as has been reported in the presence of stress (Cham et al., 2008b; Jones et
al., 2013). We found that the effects of task on visual processing time and response accuracy were fairly similar between groups, possibly because the acuity demands of the visual targets used in our study were low. Also, no feedback was provided regarding subjects’ performance in the discrimination task. Thus, it seems that our participants had likely exerted a low level of “effort to see,” a factor which has been suggested to alter INS parameters, rather than the task demands alone (Tkalcevic & Abel, 2005; Cham et al., 2008b; Jones et al., 2013). The minimum size of visual targets used in our study was above INS subjects’ visual acuity threshold in both the current study and the study by Dunn et al. (2015). Further studies are required to address this limitation by using targets which approach participants’ limits of resolution.

Although foveation time contributes to both target acquisition time and NAFX, a formula that uses INS waveform to objectively estimate potential visual acuity in the absence of any sensory defect in patients with INS (Dell’Osso & Jacobs, 2002; Dell’Osso & Wang, 2008), no significant relationship has been found between the changes in target acquisition time and NAFX due to surgical alterations in foveation (Wang & Dell’Osso, 2008). Instead of measuring visual acuity, we investigated correlations between changes in the accuracy of subjects’ responses in a discrimination task with changes in target acquisition time or total exposure time induced by mental load. Although within-subjects analysis of variance for both groups showed similar effects of mental load on visual processing time and on response accuracy, the results of the between-subjects correlations varied across groups. In contrast with the normal group where there was a trade-off between speed and accuracy of task performance, degraded task performance in the INS group was not related to changes in visual processing time or total exposure time. This was possibly because visual processing time may be more efficient in normal controls than in individuals with INS. Both groups can have similar processing times, but may use different mechanisms to resolve target details such as the integration of visual samples obtained from sequential foveation periods in INS, as opposed to continuous fixation duration in normal individuals (Dell'Osso, 2014; Dunn et al., 2014; Dunn et al., 2015). Our finding of no significant correlation between changes in total exposure time and response accuracy from low to high mental load agreed with the notion that visual task performance in INS is a multifactorial process, and extended foveation time does not guarantee an improvement in visual task performance up to the normal level (Bedell & Loshin, 1991; Dunn et al., 2014). Besides INS oscillations, other factors including underlying sensory deficit can affect visual performance to a
varying extent among INS subjects (Hertle & Dell'Oso, 2013b; Dunn et al., 2014); that might be as many patients with visual impairments. Indeed, visual function can be improved in the absence of any significant change in INS parameters (Huurneman, Boonstra & Goossens, 2016a). Recent studies showed that visual training resulted in better visual acuity in INS, and that visual acuity was associated with improved visual function in a daily task; i.e., font size in a reading task; however those improvements in INS visual function were found in the absence of any significant change in INS parameters such as fixation stability (Huurneman et al., 2016a; Huurneman, Boonstra & Goossens, 2016b, 2016c). Our results and the findings of the previous studies agreed with the notion that a task-induced change in visual function in INS is not attributed solely to visual processing time or INS oculomotor behavior such as fixation stability.

Both our current results and the previous ones by Wang and Dell'Oso (2007a) found that participants with INS have longer saccade latency and target acquisition time when compared to normal controls under the same task conditions. The difference between groups for subjects’ reaction time was similar to the differences between groups for target acquisition time: approximately 134 msec in our study. We found that both saccade latency and target acquisition time increased in the INS group as compared with normal controls. Dunn et al. (2015) reported longer reaction times for INS than controls, while saccade latency was approximately 60 msec longer in INS than controls, and saccade duration was statistically similar between the groups. Targets were displayed 3° away from center vertically as opposed to our target steps, which were ≥15° horizontally. The cumulative effect of slowed saccade execution has the potential to significantly impair performance in busy visual environments such as when playing sport (Dunn et al., 2015). Wang and Dell'Oso (2007a) suggested that increased saccade latency in INS alone, is not sufficient to result in being slower to see. In agreement with Wang and Dell'Oso (2007a), our results showed that individuals with INS are slow to respond to visual targets, mainly due to a delay in target acquisition time.

Using computer simulation, Wang and Dell'Oso (2007a) found that target acquisition time could increase in a patient with INS, if the time of the target step was during or close to the intrinsic saccades within a cycle. However, we did not find a significant correlation between stimulus time within a cycle (Tc%) and target acquisition time for individual INS subjects or for specific waveform types, regardless of the task. A further study with a larger sample size and
trials that can allow the accumulation of sufficient data for plotting Tc% versus target acquisition time for each INS waveform type or individual participant could better investigate this relationship. Other factors besides stimulus time can contribute to delay in target acquisition time in INS, such as an ongoing interaction between saccade and fixation subsystems, and changes in strategies for target acquisition using reflexive saccades, changes in INS waveform, or a combination of both (Wang & Dell'Osso, 2007a). Although we did not find any significant task-related changes in the probability of using prosaccades by individuals with INS for target acquisition, we found that the gain of prosaccades changed more in the INS group than in normal controls, and tended to decrease with high mental load in INS. It has been found that the effects of task repetition on a saccade task, i.e. a decrease in saccade latency and an increase in saccade gain, were quite similar between INS and normal controls (Huurneman et al., 2016a). Thus, our findings for the changes arising from mental load in saccade latency, which increased for both controls and INS group, and saccade gain, which decreased in INS group when compared to controls, cannot be due to familiarity with the saccade task. As discussed in chapter 3 for normal subjects, mental load can disrupt the attention allocated to the post-saccade task, and increases saccade latency and decreases saccade undershoot (Kapoula & Robinson, 1986; Pashler et al., 1993; Roberts et al., 1994; Duncan et al., 1997; Corbetta et al., 1998; Stuyven et al., 2000; Simon et al., 2002; Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005; Irving et al., 2009; Guyader et al., 2010; Van Stockum et al., 2011). Intrinsic saccades during a nystagmus cycle, and visual guided saccades, share similar neural pathways (Worfolk & Abadi, 1991). It has been suggested that programming of the quick phase of INS can interfere with accurate programming of the gain of prosaccades (Wang & Dell'Osso, 2007a). A study of oculomotor behavior in INS using simulated pendular nystagmus waveforms has suggested that the slow phase of INS affects the amplitudes of prosaccades (Jacobs & Dell’Osso, 2004). As also shown by our results, the extent to which INS oscillations disrupt the accurate programming of saccade size can be idiosyncratic, probably due to variations in the INS cycles. Variations in saccade gain could also contribute to target acquisition and reaction times varying more in INS subjects than controls. Probably, the interference of INS with the accurate programming of prosaccades exacerbated under mental load; and thus, the effect of mental load on programming the size of prosaccades was greater in INS than controls. Although saccade gain, and thus target acquisition time, varied more within INS subjects than controls, changes in those variations from low to high mental load were similar
between the groups. In the present study, mental load decreased the averaged gain of prosaccades in INS, while target position was reached by increased use of changes in INS waveform, i.e., slow phase of INS cycle rather than using prosaccades. A behavioral model suggested that INS waveforms can be caused by an abnormality in the ocular motor system that originates from smooth pursuit eye movements, or less common vestibular eye movements (Dell'Osso & Daroff, 1975; Jacobs & Dell’Osso, 2004). The results obtained from former studies in our lab suggested that the interaction between slow eye movements and brain areas which are linked with attention, motivation and cognitive processes, such as the frontal cortex, cingulate cortex and amygdala, can make INS worse (Tkalcевич & Abel, 2005; Cham et al., 2008b). Probably, that interaction may affect the gain of prosaccades and enhance slow eye movements for target acquisition under a high mental load condition. However, further studies are required to ascertain this.

7. Conclusion

To see an object, we need to not only place its image on the fovea, but also process the resulting visual input after the information has been collected. The results of the current study and previous findings showed that INS subjects take longer than normal subjects to respond to a visual object, both in the absence and presence of internal states such as high mental load (Sprunger et al., 1997; Jones et al., 2013). We showed for the first time that the change in saccade latency; i.e., the timing aspect of a saccade execution, due to mental load is similar between normal subjects and INS subjects. However, the effects of mental load on programming the size of prosaccades varied between those with INS and normal controls. We suggested that the contribution of the INS slow phase is favoured over the prosaccade to acquire a new target position under high mental load. Our results showed that the phenomenon of being slow to see in INS can be attributed to later target acquisition, and hence, delayed visual sampling across tasks. We found for the first time that total exposure time and visual processing time can remain almost unchanged with high mental load but the efficiency of visual processing probably decreases further with the effort to see in patients with INS than in normal subjects. In contrast to controls, reaction time worsened; i.e. increased more, in patients with INS when they performed a visual.
task while under a high mental load. The possible reason is that both target acquisition and visual processing times increase from low to high mental load in INS subjects when compared to controls.

When evaluating patients clinically or when considering assessing the success of treatment, these results should be kept in mind. The real world is more complicated than common clinical settings, and demands various levels of mental engagement. To compare pre- and post-INS therapies, not only static visual acuity, but also the accuracy and speed of subjects’ responses to visual targets, should be measured with mental loads resembling real world conditions.
Chapter six: General conclusion

It has been frequently stated that INS gets worse under internal factors such as stress, visual attention, and mental concentration (Dell'Osso et al., 1974; Dell'Osso, 1982; Abadi & Dickinson, 1986; Evans, 1988; Abadi & Scallan, 1999; Abadi & Scallan, 2000; Abadi & Bjerre, 2002). Apart from the studies by Tkalcevic and Abel (2005) who did not find any change in INS parameters, and Wiggins et al. (2007) who found INS parameters improved; i.e., foveation time increased and INS intensity decreased at the threshold level of resolution acuity, few studies quantified the effects of internal states on INS (Cham et al., 2008b; Jones et al., 2013). The latter found that stress exacerbated INS; that is, foveation time decreased and INS intensity increased.

Although INS parameters usually change with gaze position, all of these studies were limited to either the primary or the null position (Wiggins et al., 2007; Cham et al., 2008b; Jones et al., 2013). Both gaze position and internal state are important factors that need to be considered when evaluating INS (Abadi & Dickinson, 1986). However, no previous study has investigated the effect of internal states at different gaze positions in INS.

This thesis, the first in the literature, measured the effects of mental load on INS at, and some distance away from, the null. We showed that a change in foveation from baseline due to cognitively induced stress is larger at the null position than away from the null. The baseline task was set by looking at a fixation point, which imposes no visual acuity demand. Simple targets such as LEDs or dots on a screen, as implemented in this thesis, are widely used when evaluating INS pre- and post-treatment. This is done expressly to minimise visual demand. Our results suggest, for the first time, that the contribution of foveation to visual function can vary with both gaze position and task. The use of a simple, visually undemanding target, and ignorance of internal states such as mental load when recording INS, may result in misestimating visual function through indices such as the expanded nystagmus acuity function (NAFX), which is actually designed to predict the best potential visual acuity prior to INS therapy (Dell'Osso & Jacobs, 2002; Wang & Dell'Osso, 2009). However, this hypothesis would require further exploration, as there is contradictory evidence in the literature for the effect of visual acuity demand alone on INS (Tkalcevic & Abel, 2005; Wiggins et al., 2007; Cham et al., 2008b). In addition to gaze position, task demands should be considered when evaluating INS parameters.
and visual task performance in patients with INS. Real world conditions are a complex mixture of mental and visual demands. Clinical measurements in patients with INS are more likely to overestimate visual function beyond what is experienced in daily tasks, if mental workload is not considered. We found mental load is more likely to worsen foveation at the null position without an increase in INS frequency. Our results showed that the decrement in visual task performance due to mental load is greater at the null than away from the null. According to our findings (chapter 4), the total exposure time required to resolve target details at the null position could be more likely acquired through an increase in the target viewing time; this might result in task performance worsening in INS subjects with stress due to shortage in viewing time.

In order to have a clear view of a visual object, we first need to get the eye on the target of interest to collect reliable visual samples, and then process collated visual information; this process, however, does not have a clear time distinction and thus one cannot infer whether visual processing occurs after visual sampling or simultaneously. Subjective claims by individuals with INS have stated that they recognise visual objects late (Sprunger et al., 1997). Therefore, another area of interest for this thesis involves examining the effect of internal states on the common subjective impression among individuals with INS; i.e. being “slow to see”. To better investigate the phenomenon of being slow to see in INS, we ran a saccade experiment in patients with INS and normal participants, with and without a high mental load. For normal participants, we found that high mental load resulted in longer saccade latency, and consequently, longer target acquisition time. We have explained our findings as being due to the limited capacity of information processing resources; shown by a slow rate of rise in the saccade decision signal in the LATER model analysis of latency (Chapter 3). Our results agreed with previous studies indicating that saccade tasks can be interrupted by a supervisory system in the presence of a disruptive secondary task (Stuyven et al., 2000; Harwood et al., 2008). For normal-sighted individuals, control of the target acquiring system by the supervisory attentional system can explain interference with the execution of prosaccades by another task, and thus the late target acquisition time. We suggest that the generation of secondary saccades decreases if individuals are less attentive to a post-saccade visual task due to a concurrent mental activity. However, the final saccadic end position and target viewing time can remain unchanged. We agreed with the notion that visual performance can be disrupted by internal states, due to poor visual processing instead of a shortage in visual processing time. In other words, mental disruption by a concurrent
cognitive task can make individuals less attentive to the visual task, and result in more response
ers, with no significant change in visual processing time. However, it might differ for
individuals with INS for whom stable visual sampling is limited to foveation times. Both target
acquisition time (Wang, Dell’Osso, Jacobs, et al., 2006) and the viewing time required to resolve
target details (Jones et al., 2013) can be influenced by foveation time in INS, which itself is
affected by stress (Cham et al., 2008b; Jones et al., 2013). Therefore, there was a possibility that
the effects of stress on target acquisition time and visual processing time differed between INS
subjects compared to normal subjects. For the first time in the literature, this thesis investigated
the effects of internal states on saccade tasks in both INS and controls (Chapter 5). We found that
changes in saccade latency due to mental load were similar between INS and normal subjects.
Our results agreed with the notion that visual processing time in INS does not significantly differ
from normal controls (Dunn et al., 2015). We agreed that longer target acquisition time, and
hence delayed visual sampling in individuals with INS as opposed to normal controls, can be
responsible for feeling slow to see in INS (Wang & Dell’Osso, 2007a; Dunn et al., 2015); we
showed that is also true in the presence of mental load. According to our results, the phenomenon
of being slow to see worsens with mental load in INS, even in the presence of similar viewing
time and total exposure time. Target acquisition time and the subsequent viewing time needed to
collect and process visual information, defined as visual processing time in this thesis, contribute
to longer recognition time in INS (Wang & Dell’Osso, 2008; Jones et al., 2013; Dunn et al.,
2015). It seems that the extent to which INS affects the timing aspects of visual function depends
on task demands, e.g., detection, acquiring a target or solving target details. Our findings
demonstrated that the increase in target acquisition time due to task conditions is greater in INS
subjects than in normal-sighted subjects. In addition, we found that the change in visual
processing time with a high mental load, after target acquisition, varies between normal and INS
subjects. Longer target acquisition time with no decrement trend in the target viewing time,
unlike what was shown for controls, contributed to the fact that individuals with INS took
significantly longer time to respond to visual objects when under a high mental load, as opposed
to controls.

No relationship was found between total exposure time or processing time and the accuracy of
subjects’ responses, thus agreeing with earlier findings that extended foveation does not
guarantee an improvement in visual task performance up to normal levels (Bedell & Loshin,
1991; Dunn et al., 2014). Time restriction has been found to decrease the visual acuity threshold more in individuals with INS than in normals (Yang et al., 2005). We suggest that the efficiency of visual processing time is further decreased with stress in INS. Visual task performance in INS is a multifactorial process, and individuals with INS use different mechanisms from normal subjects to resolve target details.

Both accuracy and speed of visual task performance are important when dealing with various levels of workload in real world conditions. An increase in target acquisition time within both normal and INS subjects can indicate a decrement in post-saccadic task performance under mental load. For low acuity demand targets, as used in this thesis, accuracy of task performance can be similar between normal and INS groups. In contrast to normal subjects, for whom reaction time in visual tasks can remain unchanged even under mental load, slowness in visual task performance due to mental load can be shown for individuals with INS. This finding can be critical in terms of tasks in which speed of performance is critical; e.g., driving in the rain.

This thesis attempted to show that for assessment of visual function in INS, e.g. when evaluating outcomes of INS therapies, the accuracy and speed of subjects’ responses to visual targets should also be measured at various gaze positions and under mental loads resembling real world conditions. We showed that eye movement recording while looking at simple and visually undemanding targets, as commonly reported in the literature, cannot represent all aspects of visual functioning in INS and might result in the overestimation of visual performance in patients’ daily lives. Finally, we suggest adding both target acquisition time and subjects’ response time to evaluate visual function in INS.

Limitations and further studies

We attempted to investigate the effect of cognitively induced stress using visual and mental tasks. However, our minimal stimulus size was limited by the low-resolution projector available at the time. Hence, the acuity demand level of visual targets used in our experiments was not high. Probably without this limitation, total exposure time and target viewing time (i.e., visual
processing time) would have increased under stress in our INS group. In both the acuity and saccade experiments, no feedback was provided for the accuracy of subjects’ responses. Our findings in chapter 4 did not show any main effects of task on INS parameters. However, we found that an interaction between task and gaze position affected foveation time. We believe our experimental protocol for the restricted condition succeeded in presenting a difficult visual task; however, the level of visual effort to resolve target details was not great. Although cognitive-induced stress was confirmed with physiological measurements in both normal and INS groups, it seems that our participants exhibited a low level of effort to see, a factor that has been suggested to alter INS parameters rather than the task condition alone (Dell'Osso et al., 1974; Dell'Osso, 1982; Abadi & Dickinson, 1986; Abadi & Scallan, 2000; Abadi & Bjerre, 2002; Scheiman & Wick, 2002; Tkalcevic & Abel, 2005; Cham et al., 2008b; Jones et al., 2013). Due to the same hardware limitations, we were not able to measure contrast sensitivity or visual acuity, considered as minimum angle of resolution at 100% contrast. In order to decrease the visibility of the targets when we could no longer reduce their size, we compensated by decreasing contrast to increase visual demand for the experiment described in chapter 3 and 4. While decreasing both size and contrast made target details harder to resolve, it is not clear if small targets at 100% contrast would produce the same effects on INS as larger, low contrast targets. Disambiguating this will require further studies using higher-resolution displays.

Another explanation for not observing significant main effects of task on INS parameters (chapter 4), total exposure time and visual processing time in INS (chapter 5), might be the sample size. Using 11 patients with INS for chapter four, the current study was suitably powered to detect a minimum required mean difference of 11 units in the main effects, for 2-way and 3-way interactions. We acknowledge the sample size of INS group as a limitation of this study. However, our experiments succeeded in addressing the main hypotheses of this thesis including finding that task-induced changes in INS varied at different gaze positions, and that the effect of mental load on visual recognition time is greater in individuals with INS than in normal subjects. We showed an interaction between mental load and gaze position for both percent foveation time and visual task performance (chapter 4). We analyzed task performance using a non-parametric equivalent to repeated measurements ANOVA for factorial layouts. This method has good small sample performance properties and allows for the assessment of interaction effects between within-subjects factors (Brunner, Dette & Munk, 1997; Brunner et al., 1999; Noguchi et al.,
We also showed that high mental load increased saccade latency and target acquisition time in both INS and control groups, with an interaction between task and group for the gain of prosaccades, target acquisition time and subjects’ reaction time. We suggested that an interaction between mental load and underlying INS mechanisms led to an increase in reaction time with high mental load in INS when compared to controls (chapters 3 and 5). A further study may help to clarify this relation. Target presentation time varied between our tasks. Thus, a further study with larger sample size could compare the total exposure time required to resolve target details at acuity threshold level, for INS subjects across tasks with similar target viewing time but different mental loads.

Measuring eye movements in a clinical environment clearly may not include all aspects of what individuals with INS experience in the real world. To address this limitation, a further study could compare individuals with INS to normal controls while carrying out more nearly “real world” tasks under different levels of mental load. An example of a daily task with a high mental load could be a shopping trip to an unfamiliar store during which a customer is required to find and read finely printed ingredients of a new product in a limited time. Alternatively, participants could be required to locate the next train to a specified destination at a busy station when running late. During these tasks, eye movements could be recorded using a portable eye tracker while a heart rate monitor, as used by athletes, could determine physiologically the level of induced mental load.

Despite the limitations described above, which hopefully will be addressed in further investigations, the current thesis aimed to contribute to understanding INS and make further progress in this area, in spite of a frequently cited admonition by a distinguished neuro-ophthalmologist Wilbrand to “never write about nystagmus, it will lead you nowhere” (Wartenberg, 1953; Daroff, 2002).
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