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Sensorimotor integration processing in Diabetic Retinopathy and Diabetic Peripheral Neuropathy

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Abstract

This research study was divided in two main parts with the purpose of evaluating the direct link between visual perception and related motor output responses under different conditions of simulated reality: 1) during an optic flow stimulation which induced a perception of forward movement, and 2) during a driving task using a simulator. The experiments focussed on the evaluation of two different complications of diabetes: diabetic retinopathy and diabetic peripheral neuropathy (DPN). This thesis describes two experiments conducted in order to evaluate the different contributions of both central and peripheral nervous factors in affecting the sensorimotor integration process in diabetes.

Study I. The aim was to assess how optic flow processing contributes to the control of posture and whether it requires the predominant activation of cortical networks involved in motion perception or the intervention of subcortical loops.

We recruited thirty-four volunteers with differing retinal functionality: 13 people with early-stage retinopathy (Retinopathy group, average age 63 ± 12), 8 people who had undergone laser treatment on the peripheral retina (Laser group, average age 56 ± 15) and 13 healthy subjects (Control group, average age 59 ± 9). The experiments were performed in the dark using surface electromyography (EMG) and stabilometry. EMG data were recorded bilaterally from the anterior tibialis and soleus while subjects stood on two Kirstel force platforms in order to record the centre of pressure (COP) parameters: antero-posterior (AP), medio-lateral (ML), speed and area. Stimuli were presented on a screen covering 135 x 107° of the visual field. Stimuli were radial optic flow stimuli presented full field, in the foveal or in the peripheral portion of the retina. To discover the role of optic flow direction in postural stability, we also manipulated the spatial distribution of dot speed to simulate specific heading directions. We acquired 5 trials per stimulus for 30 seconds each. Fixation in the dark was used as baseline.

A repeated measures ANOVA was performed on the normalized EMG and COP parameters, with side (right/left) as the within-factor and group and stimuli as the between-factors. We found significant differences between groups in all COP variables ($p<0.001$). A main effect of "Side" and an interaction effect of "Group x Side" were found for COP_{ML} ($p<0.001$), COP_{Area} ($p=0.010$) and COP_{Speed} ($p<0.001$). The EMG analysis showed a significant main effect for "Group" ($p<0.001$). Post-hoc test showed a significant difference between Control and Retinopathy ($p<0.001$) groups and Laser and Retinopathy ($p=0.002$) groups.

People with retinopathy and people who had undergone laser treatment showed a higher postural instability compared to control subjects. Differing retinal functionality produced different postural strategies, while changing optic flow stimuli did not. Based on these findings, postural control seems to be a process dependent on perceptual analysis via feed-forward cortical circuits.

Study II. The aim was to assess whether diabetes was associated with alterations of visual gaze behaviour and/or neuromuscular impairment that might adversely affect driving performan**c**e.

Fifty-four active drivers, 15 with Diabetic Peripheral Neuropathy (DPN, average age 66±6.0), 25 with diabetes but no neuropathy (DM, average age 62±8.7) and 14 control subjects without diabetes (Control, average age 58±10) undertook a driving task using a driving simulator while eye movements were recorded using a ASL500® eye tracker. Cross-correlograms of horizontal eye vs steering wheel movements were generated using a Spike2® script in order to evaluate eye-steering coordination (r^2%). Together with these measures, a maximum isometric test of the plantar flexor muscles and a proprioception test of the right ankle joint using a dynamometer (Cybex®) were performed. We analysed the rate of torque development (RTD, Nm/s) as the gradient of the torque-time curve over a defined period of time (150 ms) from the onset of contraction, and the ankle proprioception "error value" (degrees), and we compared these with some measurements of car pedal control (degrees).

A univariate ANOVA analysis revealed a significant "Group" main effect for eye-steering coordination values (r^2 %) ($p=0.013$) and for the rate of torque development (RTD) values, ($p<0.001$). The Bonferroni post-hoc tests demonstrated that the Control group differed significantly from both DPN ($p=0.038$) and DM groups ($p=0.028$) in the eye-steering coordination values. At the same time, RTD values in the Control group were higher compared to both DPN ($p<0.001$) and DM ($p=0.011$) groups. Proprioception showed a significant effect for "trial" ($p=0.009$), and "error values" decreased during a three trials session.

The potential for impaired driving performance with diabetes seems to be represented by diminished eye-steering coordination. While proprioception function seems to indicate the potential for improvement, a slower production of strength (RTD) in the plantar flexor muscles seems not to influence accelerator pedal control during a driving simulation task in people with diabetes (with and without DPN).

These results confirm the role of visual perception and eye movements in guiding human movements during dailylife activities. In particular, we demonstrated the detrimental effects of diabetes and the different contribution of diabetic retinopathy and diabetic peripheral neuropathy in affecting both central and peripheral components of the sensorimotor integration process.

1. INTRODUCTION

Most movements are under continual sensory guidance. The dominant sense in control movements is vision and one of the central problems in neuroscience is to understand how the brain could use visual input to control whole body movements and how they are combined with the other sensory inputs in order to perform to the majority of daily life activities [1].

During our daily life we are continuously exposed to optic flow patterns which provide crucial information about self-motion and environmental structures [2]. Gibson firstly introduced the concept of "optic flow", as the self-movement perception we experience when we are walking or driving [3]. He noticed that the visual motion in the "optic array" surrounding a moving observer radially expands out of a singular point that has the fundamental role in heading perception. He termed this point "focus of expansion" (FOE) (Fig.1).

In the nervous system, retinal stimulation related to self-motion is integrated with other somatosensory information signals, in order to assess direction and speed of self-movement, guide locomotion, and/or maintain the correct posture [4]. Somatosensory inputs derive primarily from the forces and motions exerted by the feet on the support surface, vestibular inputs derive from head motions, related to active or passive body sway in response to gravity, and visual input derives from sway-dependent motions of the head subsequent to the surrounding visual input [5]. Specific spatial and temporal properties of the optic flow, such as geometric structure [6, 7], amplitude [8, 9], velocity [10-13], frequency [10, 11] and location in the visual field (foveal or peripheral) can influence such postural responses [13-15]. The neural mechanisms integrate visual, vestibular, and proprioceptive inputs of self-motion perception to generate the typical body oscillations defined as body sway. Indeed, numerous studies have observed that stimulation of such systems, visual [16-18], proprioceptive [19] or vestibular [20] evoke body sways. These small postural oscillations

reflect the regulatory activity of several control loops (feedback and feedforward mechanisms) responsible for the maintenance of postural balance [21].

Few studies have shown that optic flow stimuli are crucial for the maintenance of quiet stance in the upright position when integrated with the other sensory signals [8]. Visual input changes, such as from forward to backward motion or from dark to light environment, require an updating of sensory integration to provide the premotor and motor cortices with precise and reliable information about both the extra-personal environment and internal state [9, 22]. So, what might appear to be a simple directed action consists of several independent but interconnected contributing factors [23].

Every simple movement involving the central nervous system uses information arriving from the peripheral nervous system about a vast array of sensory receptors to ensure the correct pattern of muscle activity. Sensory information from muscles, joints and skin are transmitted by different types of sensory neurons and converted into parallel pathways to the primary somatosensory cortex, where all afferences are combined into a unified somatic percept [1].

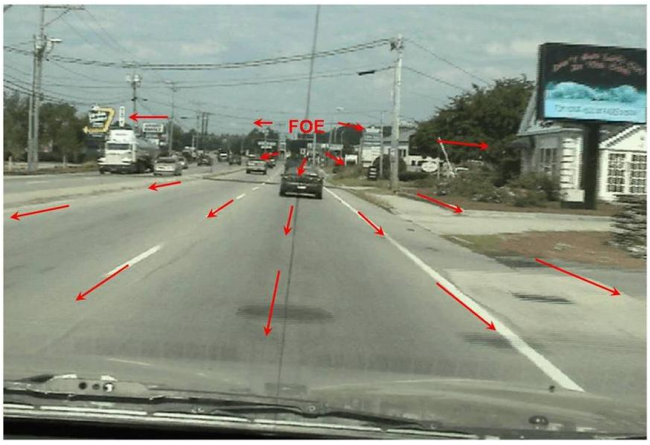


Figure 1: The focus of expansion (FOE), the single central point at which optic flow seems to originate corresponds to the final destination of self-motion.

2. OPTIC FLOW

Optic flow corresponds to changes in the optic array induced by the relative motion between the subject and the environment [3]. Information about optic flow is indispensable for encoding direction of heading, orientation, and visual navigation in three dimensional space [3]. Optic flow becomes fundamental in controlling posture and locomotion, for the perception of moving objects, and the selection of motor actions that allow the appropriate interaction with them [17]. Any transformation of the total retinal image, as distinguished from a part within it, tends to yield an experience of a movement for the observer, and the kind of movement experienced depends on the kind of transformation. If we assume an immobile observer, such as under experimental laboratory conditions, expanding optic flow would indicate that a surface is approaching and would provide information on the direction of its approach [24].

During daily life, most natural behaviour is accompanied by eye movements, which disrupt the retinal projection in order to direct the gaze towards objects and maintain stable vision. The motion of an object, the movement of the eye and the movement of the observer himself contribute to alter the image projected on the retina [25]. The result is a retinal motion pattern that is composed of translational (body movements) and rotational (eye movements) components [2]. In the complex process of heading detection for translational motion (motion parallax), the visual speed of each element is inversely proportional to distance; in contrast, rotation induces equal angular speed in all image points independent of distance. So, motion parallax becomes fundamental to extrapolate translational movement to rotational movement.

In the parietal cortex, there are selective neuronal receptive fields that are modulated by eye position. Indeed, the movement of an object in the visual field with the head remains stable because parietal cortex neurons use the information from the retina and the eye movements to maintain a stable head-centred representation of the visual field. Similarly, in the ventral premotor cortex and

parietal cortex, specific neurons combine information about posture, eye and head movements to establish the body-centred frame of reference [1]. Information about the positions of the retina relative to the head and body might come either from mechanoreceptors in the ocular muscles controlling the positions of the eyes (a proprioception or "inflow" from the periphery to the brain), or from internal monitoring of innervations sent to those muscles (an efference copy or "outflow") from the brain to the periphery [26].

The visual system may detect eye rotation, either by visual means or through an oculomotor efference copy [25] and removes the visual consequences of the rotation from the internal representation of the flow field. The question of whether this 'retinal flow' alone allows the brain to estimate heading, or whether additional "extraretinal" eye movement signals are needed, remains controversial [2]. We can conclude by saying that it cannot be assumed that a movement is the same thing in the object, the retina, the brain and consciousness, because vision motion is a sensory variable of experience [27].

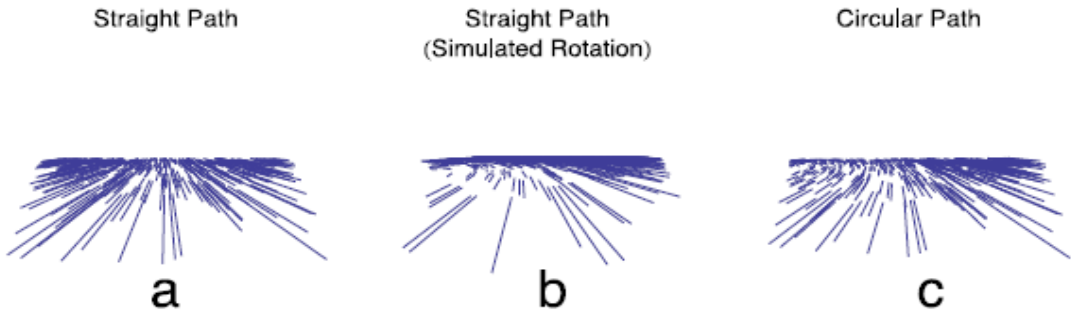


Figure 2: **Exemplar first-order optic flow fields. a) Radially expanding optic flow experienced by an observer travelling along a straight path. The optic flow contains the focus of expansion (FOE) on the horizon which indicates the heading direction. b) Movement of an observer along a straight path, as in "a", but with a constant amount of rotation added to the first-order optic flow (simulated rotation condition). Subjects that view displays with simulated rotation report travelling along a circular path. c) First-order optic flow experienced by an observer travelling on a circular path whose gaze is along the heading or tangential to the circular path). (From Layton et al., 2014).**

2.1 OPTIC FLOW PROCESSING

It has been demonstrated that in primate cerebral cortex there are neurons in multiple brain regions that can analyse different aspects of optic flow which are involved in the analysis of motion and spatial encoding [28]. Optic flow processing [29] travels through the cortico-cortical connection to the pre-motor and motor cortex at which level the motor programme is processed [30]. The exact cortico-cortical pathways of optic flow stimuli are not well understood yet. However, looking at the different onset times of the neuronal change activity we can recreate an ideal progression of neural activation, which extend from temporal to parietal and to frontal areas.

Studies in the macaque monkey indicate that about half of the cortex is involved in visual processing [31], and about 90% of projections from the eyes are channelled through the lateral geniculate nucleus (LGN) to the primary visual cortex (V1) (Fig. 3). The visual input processing is disseminated from V1 to various extra-striate visual areas for further analysis. Extra-striate areas such as V4 and the middle temporal (MT) area project directly to visual areas in the parietal and frontal lobes that are implicated in attention, working memory and motor planning. Furthermore, optic flow stimuli responses have been described in MT area [32], the medial superior temporal (MST) area [33-36], the ventral intraparietal area (VIP) area [37], and the anterior superior temporal polysensory area (STPa) [38]. This progression, at the same time as seeming to show an increased specificity to moving visual stimuli, demonstrates thus that in the MT area and the 7a area most of the cells respond to multiple kinds of optic flow stimuli, in contrast to the cells of the motor cortex, where 73.7% of cells are very selective and respond only to one type of stimulus motion [24].

MST neurons are selective for the position of the FOE and tuned for different speeds, encoding heading during different types of self-motions. What is more, their connections to the subcortical centres of gaze stabilization are fundamental for the control and guidance of eye movements [28, 34]. The MST area, which seems to be involved in the analysis of heading

perception in the far extra-personal space, directly projects to the intraparietal sulcus, which is responsible for analysing close extra-personal space.

In the VIP area, we found a selectivity for direction and speed of moving visual stimuli [37]. In particular, the inferior parietal lobule 7a area has been considered an important associative node involved in visual motion processing. It has been shown that in primates, area 7a of the posterior parietal lobe, together with the motor cortex, plays a role in visuomotor coordination, and is engaged in a wide variety of sensorimotor processes in responses to visual moving stimuli [39]. Area 7a has a preference for stimulus location 2.5 times greater than that of the motor cortex where there is a higher responsiveness to stimulus motion effect [24]. Compared to MST, it presents receptive fields (RF), the size of which doesn't vary with stimulus eccentricity [40].

The superior temporal polysensory area (STP) receives projections from both the MST area and 7a area for objects and self-motion [41]. For this reason, it seems that the STP area could have a accessorial role which contributes to integrating information about the control of forward locomotion [38].

The superior parietal lobule (PEc area) is considered to a be a division of the somatosensory system and to take part in the visuomotor integration process that integrates visual stimuli and hand movements. The PEc area responds to forward and backward body movement and as for MTS and VIP, from which it receives projection, presents a selectivity for the FOE position with respect to the fovea [42]. In addition to these areas, motor cortex M1 is involved in several aspects of movement initiation and control, including the motor command itself as well as the process interposed between a stimulus and the response to it [43, 44].

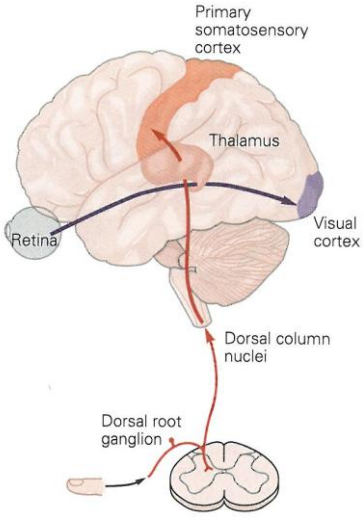


Figure 3: Somatosensory information from the dorsal root ganglia reaches the ventral posterior lateral nucleus, which relays it to the primary somatosensory cortex. Visual information from the retina reaches the lateral geniculate nucleus, which conveys it to the primary visual cortex, in the occipital lobe.

3. FROM PERCEPTION TO MOTOR ACTION

Sensory information representing different modalities converges upon areas of cortex that integrate information into a polysensory event. The posterior association areas that process this sensory information are highly interconnected with the frontal association areas responsible for planning motor actions. Sensory pathways dedicated solely to visual, auditory, or somatic information converge in multimodal association areas in the prefrontal, parieto-temporal, and limbic cortices (Fig.4). Neurons respond to combinations of signals representing different sensory modalities by constructing an internal representation of the sensory stimulus concerned with a specific aspect of behaviour. Simple movements as well complex motor actions derive from the pattern of firing of large networks of neurons in the frontal lobe. The final motor pathways leaving the cerebral cortex originate primarily from the primary motor cortex, which occupies the precentral gyrus. Neurons in this area fire just before a group of muscles contract to move a joint in a specific direction. The premotor cortex, a set of interconnected areas in the frontal lobe just rostral to the

motor cortex, includes areas 6 and 8 and the supplementary motor cortex on the medial surface hemisphere. Neurons are active during preparation of movements, and during the planning of movements far in advance of the actual motor response. The premotor cortex receives inputs mainly from three resources: 1) the motor nuclei in the ventro-anterior and ventro-lateral thalamus (which receive input from the basal ganglia and the cerebellum; 2) the primary somatosensory cortex and parietal association cortex which provide information about the ongoing motor response; and 3) the prefrontal association cortex. When the brain decides on a motor programme to perform a task it takes into account its stored experience and the external perturbations. It also gauges the importance of speed versus accuracy. The brain implements a motor programme by sending signals to the spinal cord, directly to motor neurons, or indirectly through a variety of interneurons. Most spinal interneurons receive convergent input from many somatosensory modalities and the sensory pathways include variable sensory weights that can change as environmental factors change the "sensory re-weighting" [45, 46]. External perturbation (unpredictable events) or internal perturbation due to the activity of the nervous system itself leads the nervous system, to respond in two ways. First, it monitors sensory signals and uses this information to act directly; this moment-to-moment control is based on a feedback circuit. Second, the nervous system uses the same or different senses to detect imminent perturbations and initiate proactive strategies based on experience. This anticipatory mode is called feedforward. These forms of control are refereed as closed loop and open loop depending on the sensory information that can directly or not influence the timing of the response [47]. We can say that while the feedforward circuits are important for controlling posture and movement based on motor programmes deriving from experience, a feed-back system helps to maintain the posture and a certain movement responding on inputs arriving in real time.

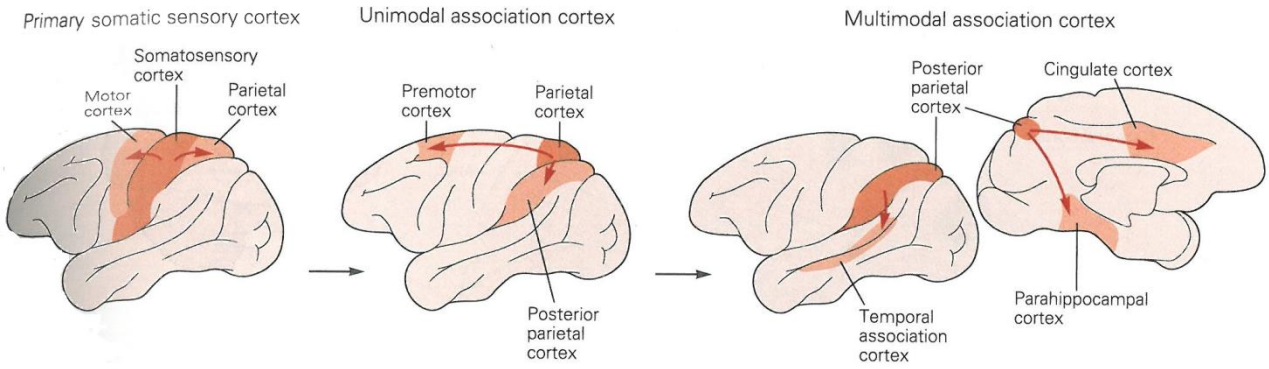


Figure 4: The processing of sensory information begins with primary sensory cortices, continues in unimodal association cortices, and is completed in multimodal association areas. In each brain the dark coloured areas indicate the origin of a projection and the light coloured areas the termination. Sensory system also projects to portions of the motor cortex. (Kandel E, Schwartz J and Jessel T (2014). Principles of Neural Science. New York, Elsevier).

4 DIABETES

The World Health Organization (WHO) has estimated that the global prevalence of diabetes for all age groups will rise from 2.8 % in 2000 to 4.4 % in 2030 [48]. Approximately 25% of individuals diagnosed with diabetes develop a polyneuropathy after 10 years. This percentage increases to 50% after 20 years and 70% at 30 years. The pattern of progression is strictly dependent on the diabetes duration and determine a high variability of manifestation. Diabetic neuropathies are complex, heterogeneous disorders that encompass a wide range of abnormalities affecting both peripheral and autonomic nervous systems, causing cardiovascular complication, nephropathy leading to renal failure, retinopathy with a potential loss of vision, and peripheral neuropathy [49]. The most disabling consequence is the impairment of the sensorimotor integration process.

Both diabetic retinopathy (DR) and diabetic peripheral neuropathy (DPN) can be considered sensory neuropathy. Diabetic retinopathy adversely affects the retina epithelium; it is responsible for an accelerated neuronal apoptosis and activation or altered metabolism of neuroretinal supporting cells leading to a progressive loss of the visual function [50]. On the other hand, diabetic

peripheral neuropathy is characterized by a diffuse damage of both sensory and motor fibres which cause a loss of the somatosensory and motor functions [51].

4.1 DIABETIC RETINOPATHY:

4.1.1 DEFINITION AND CLASSIFICATION

Diabetic retinopathy (DR) is a common and specific microvascular complication of diabetes. Clinically DR is defined as the presence of typical retinal microvascular signs in an individual with diabetes mellitus. Diabetic retinopathy occurs when the increased glucose level in the blood damages the capillaries, which nourish the retina. Diabetic retinopathy is a major cause of acquired blindness before 65 years of age in the industrialized countries in the Western world, but is also a rapidly increasing problem in urban areas in developing countries [52, 53]. Several scales are used for its assessment, but the only validated classification is the ETDRS (Early Treatment Diabetic Retinopathy Study) [54].

The prevalence of DR increases with duration of diabetes and can be classified into two stages: non-proliferative and proliferative. Non-proliferative diabetic retinopathy can be mild, moderate or severe. Proliferative diabetic retinopathy can be early, moderate, severe, complicated. The earliest visible sign in non-proliferative DR are micro-aneurysms and retinal haemorrhages. A progressive capillary non-perfusion is accompanied with development of cotton-wool spots, venous beading, and intra-retinal microvascular abnormalities (neovascularization)[55]. Proliferative DR occurs with further retinal ischemia and is characterized by the growth of new blood vessels on the surface of the retina or the optic disc. These abnormal vessel may bleed, resulting in vitreous haemorrhage, subsequent fibrosis and retinal detachment [56] (Fig. 5).

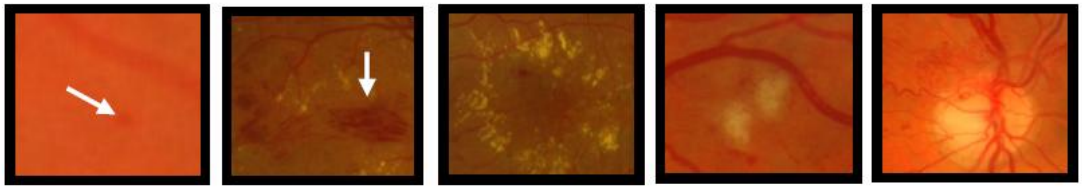


Figure 5: Fundus abnormalities of diabetic retinopathy: (a) micro-aneurysms, (b) haemorrhage, (c) hard exudates, (d) cotton-wool spots, and (e) neovascularization (Diah Wahyu S. et al. 2017).

4.1.2 PHYSIOPATHOLOGY

While differences in ethnic origin are a factor in the prevalence of diabetic retinopathy (DR) - Africans American, Hispanics, and south Asian seem to be the most affected - new emerging evidence supports a genetic component for diabetic retinopathy. Nevertheless, the results of epidemiological studies have shown that diabetic retinopathy is prevalently associated with many systemic and lifestyle factors, including obesity, alcohol consumption, hypertension, hyperglycaemia, hypercholesterolemia, inflammation and endothelial dysfunction [57, 58]. Hyperglycaemia instigates the cascade of events that leads to development of diabetic retinopathy. Hypertension exacerbates diabetic retinopathy through increased blood flow and mechanical damage (stretching) of vascular endothelial cells, stimulating release of vascular endothelial growth factor (VEGF). What is more, dyslipidaemia could have a role in the pathogenesis of diabetic retinopathy: DR severity is associated with increasing triglycerides and inversely associated with HDL cholesterol [59].

A series of factors has been proposed to be at the basis of the connection between hyperglycaemia and microvascular complications. The major causes include: polyol accumulation, formation of advanced glycation-end products (AGEs), oxidative stress and activation of protein kinase C. [60]. There is growing evidence that inflammation plays a prominent part in the pathogenesis of diabetic retinopathy [61]. In response to hyperglycaemia and other stresses, vast

array of inflammatory mediators are upregulated, triggering parainflammatory responses that might cause abnormal leukocyte interaction and ultimately retinal microvascular damage. The site of damage is the endothelium of retinal vessels; however, the traditional definition of retinopathy as purely a manifestation of microvascular damage is incomplete. The most important finding is that neuroretinal impairment might develop in the early stages of diabetic retinopathy, even before the onset of microvascular changes. This occurrence has been linked to theory that diabetes might reduce insulin receptor signalling in the retina, leading to neurodegeneration.

Diabetic retinal neurodegeneration is a progressive process induced by diabetes and characterized by neural apoptosis and reactive gliosis, an injury of the glial cell characterized by an altered metabolism of neuro-retinal supporting cells. The retinal pigment epithelium (RPE) is a monolayer of pigment cell that faces the photoreceptor outer segments and absorbs the light energy focused by the lens on the retina [62]. RPE transports ions water and metabolic end-products from the sub-retinal space to the blood; it takes up nutrients (glucose, retinol, fatty acids) from the blood and delivers these nutrients to photoreceptors. The RPE is able to secrete a variety of growth factors helping to maintain the structural integrity of the choriocapillaris endothelium and photoreceptors. What is more, RPE secretes factors that promote photoreceptor survival and differentiation. A failure of any of these functions can lead to degeneration of the retina, loss of visual function and blindness [50].

4.1.3 CLINICAL ASSESSMENT

The “Early Treatment Diabetic Retinopathy Study” (ETDRS), recognized the colour fundus photographs in seven standard fields (SSFs) as the gold standard for the detection of diabetic retinopathy, even though ophthalmoscopy is the most commonly used technique to monitor the progression of the disease [54]. Additionally, examinations of the peripheral fundus are important to avoid overlooking peripheral retinal ischemia and neuro-vascularization [63]. DR is clinically

diagnosed with the onset of ophthalmoscopic signs such as micro-aneurysms, haemorrhages, and cotton-wool spots but functional defects often precede these signs [61]. However, morphological changes that lead to blindness frequently develop without any symptoms and remain unnoticed by patients. Microvascular changes are undeniably integral to retinopathy; the retina is a vascularized neural tissue, not a network of blood vessels. So, the loss of oscillatory potentials on electroretinograms predicts the onset of proliferative retinopathy better than vascular lesions seen on fundus photographs [64]. For these reasons, early stages of diabetic retinopathy, in which microvascular abnormalities cannot always be detected by simple ophthalmoscopic examinations of fundus, would require multifocal electroretinograms (mfERG) or frequency-domain optical coherence tomography (FD-OCT) exams [65].

The mfERG provide topographical measures of retinal activity; FD-OCT measures nerve fibre layer, ganglion cell density, photoreceptor abnormalities, retinal thickness, and quantifies the extracellular space of the retina. This underlines the importance of their adoption to detect morphological and functional alterations even before microvascular abnormalities could be found under ophthalmoscopic examinations. Electroretinograms are increasingly used in order to identify visual field defects in patients with little or no-vascular retinopathy; visual field, in fact, predicts the severity of retinopathy better than visual acuity because severe diabetic retinopathy could manifest without any symptomatic visual impairment [59, 66].

4.1.4 TREATMENTS AND IMPLICATIONS

Present guidelines for the optimum eye care of patients with diabetes are tight glycaemic control and blood pressure in conjunction with laser therapy as needed. The interventional approaches can be divided into primary intervention and secondary interventions [59]. Primary interventions include lifestyle interventions and/or therapeutic approaches targeted to monitor

glycaemia, blood pressure control and cholesterol. Secondary interventions are much more invasive and include: laser treatments, vitrectomy and corticosteroids injections.

Despite the destructive nature of the laser therapy, associated with significant ocular side effects, laser photocoagulation has remained the mainstay of the ophthalmic therapy for vision-threatening diabetic retinopathy over the last 50 years [67, 68]. The main technique of laser therapies for diabetic retinopathy is pan-retinal photocoagulation. The photocoagulation acts by producing laser burns over the entire retina, sparing the central macula, to promote regression or arrest progression of retinal neovascularization, possibly by a reduction of ischemia-driven VEGF production [69]. The laser light is absorbed primarily by melanosomes within the retinal pigment epithelium, leading to coagulation of adjacent photoreceptors and retinal pigment epithelial cells that result in the formation of laser burns prevalently in the periphery of the retina. Laser scars expansion may be associated with further photoreceptor loss, retinal pigment epithelial hypertrophy, and functional loss. The annual scar expansion may increase for several years after, with additional damaging effects on the visual field. Pan-retinal photocoagulation is often associated with substantial ocular side effects, such as difficulty with light dark adaptation (25%), a small decrease in visual acuity (10%), and peripheral visual loss (5%) [70]. Even though peripheral field implications seem not to compromise appropriate orientation and mobility training of patients, peripheral visual field restriction, rather than central visual field defects in visual function, has been demonstrated to correlate with the disability index [71]. Pan-retinal photocoagulation may lead to peripheral field loss that prevents driving [67]. Laser scar grades significantly correlate with stepper brake response time and increased brake pressure standard deviation [72, 73]. Diabetic retinopathy, and in particular retinal thickness, has been shown to be significantly correlated with a higher frequency of simulator accidents but, no significant correlation was found between static measurements such as contrast sensitivity, visual acuity, colour vision and deficit in visual

perception [72]. New techniques allow reduction in visual field loss. Laser-tissue interaction is influenced by wavelength, spot size, power, and exposure time; thus, retinal damage could be reduced by changing these variables. New scientific studies supporting the retinal neurodegeneration as the main event in the pathogenesis of retinopathy are aimed at discovering the mediators involved in the crosstalk between neurodegeneration and microangiopathy with the hope of finding new therapeutic approaches in order to reduce visual deficits related to treatments [61, 70].

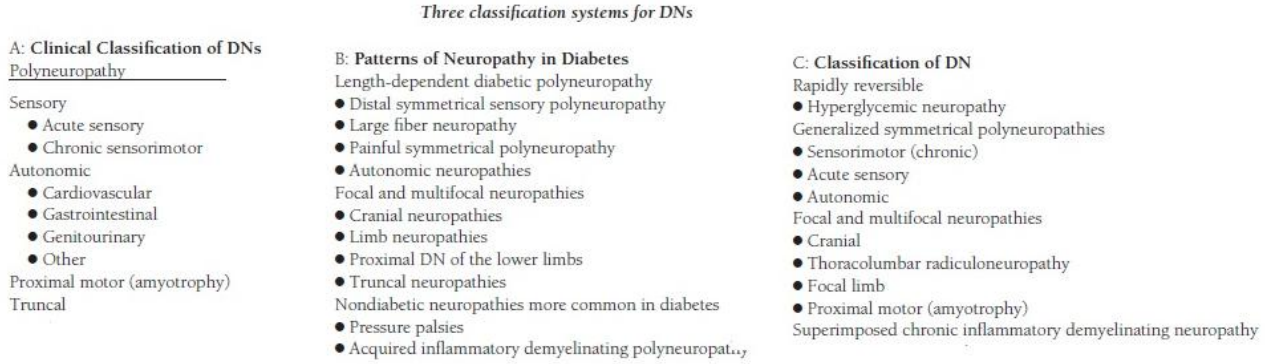
4.2 DIABETIC PERIPHERAL NEUROPATHY:

4.2.1 DEFINITION AND CLASSIFICATION

Diabetic neuropathy (DN) can be defined as the presence of symptoms and/or sigs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. It is known that neuropathy cannot be diagnosed without a careful clinical examination; absence of symptoms cannot be equated with absence of neuropathy, as asymptomatic neuropathy is very common [48].

Peripheral nerve damage is complex because it involves a variety of causative mechanisms. This may give rise to a difficulty in categorizing individual cases, taking into account the classification used by Thomas (Figure 6 C) and in particular, the most common form of neuropathy: chronic sensorimotor neuropathy (DPN) [74]. Chronic sensorimotor neuropathy is the most common manifestation of the DN that is usually insidious in onset and maybe the presenting feature in people with type 2 diabetes. It is a length-dependent process; signs and symptoms are extremely varied and are related to diabetes duration: peripheral nerve damage may occur in up to 25% of patients with diabetes mellitus after 10 years and in up to 50% after 20 years [75, 76]. Its sensory manifestations are most pronounced in the lower limbs progressing to affect more proximal parts of the body over the years. More than 80% of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder that progresses following a fibre length-dependent pattern which is characteristic of failure in fast axonal transport [77, 78]. Whereas up to 50% of patients may be

asymptomatic, 10-20 % may experience troublesome sensory symptoms. These report negative symptoms such as numbness or "feet feel dead". With regards to signs, ankle reflexes are reduced and accompanied by small muscles wasting in the feet, and also, in the most severe cases, in the hands.



Three classification systems for DNs

A: **Clinical Classification of DNs**
Polyneuropathy
Sensory
- Acute sensory
- Chronic sensorimotor

Autonomic
- Cardiovascular
- Gastrointestinal
- Genitourinary
- Other

Proximal motor (amyotrophy)
Truncal

B: **Patterns of Neuropathy in Diabetes**
Length-dependent diabetic polyneuropathy
- Distal symmetrical sensory polyneuropathy
- Large fiber neuropathy
- Painful symmetrical polyneuropathy
- Autonomic neuropathies

Focal and multifocal neuropathies
- Cranial neuropathies
- Limb neuropathies
- Proximal DN of the lower limbs
- Truncal neuropathies

Nondiabetic neuropathies more common in diabetes
- Pressure palsies
- Acquired inflammatory demyelinating polyneuropat...

C: **Classification of DN**
Rapidly reversible
- Hyperglycemic neuropathy

Generalized symmetrical polyneuropathies
- Sensorimotor (chronic)
- Acute sensory
- Autonomic

Focal and multifocal neuropathies
- Cranial
- Thoracolumbar radiculoneuropathy
- Focal limb
- Proximal motor (amyotrophy)

Superimposed chronic inflammatory demyelinating neuropathy

Figure 6: Three different clinical classifications are presented in this table. A. Purely clinical classification. B. Classification based on a mixture of clinical and anatomical findings. C. Classification based on the premise that diabetic neuropathy is not a unitary condition of disturbances in the peripheral nervous system. (From Thomas et al. 1997)

4.2.2 PHYSIOPATHOLOGY

The chronic hyperglycaemic condition seems to have a close association with abnormal cytokines production and activation of inflammatory network signalling pathways which lead to irreversible micro- and macro-vascular complications and nerve damage [79, 80]. Hyperglycaemia results in formation of advanced glycation end products (AGEs), acting with specific receptors (RAGEs), and induces monocytes and endothelial cells to increase the production of cytokines and adhesion molecules. Longitudinal data from the "Rochester cohort study" support the contention that the duration and severity of exposure to hyperglycaemias are related to the severity of neuropathy. In support to these findings, studies in patients with impaired glucose tolerance (IGT) have been providing important insights into the role of the degree of glucose dysmetabolism to the development of neuropathy [81].

4.2.3 CLINICAL ASSESSMENT

It is generally agreed that diabetic neuropathy should not be diagnosed by one symptom, sign, or test alone: a minimum of two abnormalities in quantitative sensory testing is recommended [82]. Whatever methodology is used in the assessment of neuropathic signs, it should be noted that the neurological examination of the lower limbs is the most important aspect in the clinical diagnosis of diabetic neuropathy (DPN) [81]. The use of composite scores to assess clinical signs has been widespread, since the first version by Dick et al. which used the neuropathy disability score (NDS). Further development led to a modified version of the preceding one, leading in turn to the last version of the "multi-composite Neuropathy Disability Score" (mNDS) [51]. This has been shown to be the best predictor of foot ulceration and the best neuropathic end point in a large prospective communities studies [83].

In diabetic populations, vibration, thermal, and pain thresholds have proven to be valuable in the detection of subclinical neuropathy, in tracking the progression of neuropathy in large cohorts and in predicting patients "at risk". For these purposes, quantitative sensory testing (QST) becomes fundamental. QST is defined as a procedure requiring a power source, where the intensity and characteristics of the stimuli are well controlled and where the detection threshold is determined in parametric units. QST contemplates the use of specific screening devices (Semmens-Weistein monofilament, graduate Rydel-Seiffel tuning fork and other devices) in order to identify the sensory modalities affected and to estimate the magnitude of the deficits following standardized procedures. The composite multiple disability score mNDS consists of a series of different sensorial modalities testing: 1) temperature perception, which is the ability to distinguish between a warm and cold object applied to the end of the big toe; 2) pain perception, which correspond to the ability to distinguish between a sharp and blunt object applied to the end of the big toe; 3) vibration detection, which is the ability to distinguish between a tuning fork applied to the end of the big toe that is

vibrating at 128Hz and the same tuning applied without any vibration; 4) the presence of an Achilles tendon reflex (Fig. 7). In addition to this battery of tests, vibration perception threshold (VPT) and the monofilament test are usually added [84]. The VPT involves an instrument applied to the end of the big toe with the vibration incrementally increased until the point when the person can detect the vibration. The monofilament test (Bailey monofilament, 10 g.) assesses pressure perception through gentle pressure sufficient to buckle a nylon filament. The most common algorithm recommends four sites per foot: generally the hallux and metatarsal heads 1, 3, and 5 [85].

In addition, an appropriate battery of electrophysiological tests support the measurement of the speed of both sensory and motor conduction, the amplitude of propagating neuronal signal, the density and synchrony of muscle fibres activated by maximal nerves stimulation, and the integrity of neuromuscular transmission.

	SCORE	RIGHT	LEFT
TEMPERATURE	PRESENT 0 ABSENT 1		
PIN PRICK			
TUNING FORK			
ACHILLES REFLEX	PRESENT 0 REINFORCEMENT 1 ABSENT 2		
TOTAL out of 10			

Figure 7: The presence and the severity of the neuropathy were measured using the multiple neuropathy disability index (mNDS), a composite test of multiple sensory responses. The mNDS ranges from 0 to 10, with 0 being detection of every sensation applied to the feet and 10 meaning a complete lack of sensory perception in the feet.

4.2.4 SENSORY AND MOTOR IMPLICATIONS IN DAILY LIFE ACTIVITIES

Disturbances within the somatic sensory system can be located with remarkable accuracy because there is a direct relationship between the anatomical organization of the functional pathways in the brain and specific perceptual and motor behaviours. The somatic sensory system

transmits information about four major sensory modalities: touch, proprioception, pain and temperature. Each sensory modality is mediated by a distinct system of receptors (Fig. 8) and pathway to the brain, but they share the same class of sensory neurons in the dorsal roots ganglion. Mechanoceptors and proprioceptors are innervated by dorsal root ganglion neurons with large-diameter, myelinated axons that conduct action potentials rapidly. Both temperature and pain sense are conveyed by thinly myelinated or unmyelinated fibres, which conduct impulses more slowly. Touch and proprioception ascend ipsilaterally by the dorsal column medial lemniscal system to the thalamic neurons which send their axons to the somatosensory areas in the postcentral gyrus of the cerebral cortex. On the contrary, pain and thermal sensations are not transmitted directly to the thalamus, but conveyed by the anterolateral system through direct or multi-synaptic networks using indirectly three distinct pathways (spinotalamic, spinoreticular and spinomesencephalic) [1].

Receptor type	Fiber group	Fiber name	Modality
Cutaneous and subcutaneous mechanoreceptors			Touch
Meissner's corpuscle	Aα,β	RA	Stroking, fluttering
Merkel disk receptor	Aα,β	SAI	Pressure, texture
Pacinian corpuscle[2]	Aα,β	PC	Vibration
Ruffini ending	Aα,β	SAII	Skin stretch
Hair-tylotrich, hair-guard	Aα,β	G1, G2	Stroking, fluttering
Hair-down	Aδ	D	Light stroking
Field	Aα,β	F	Skin stretch
Thermal receptors			Temperature
Cool receptors	Aδ	III	Skin cooling (25°C)
Warm receptors	C	IV	Skin warming (41°C)
Heat nociceptors	Aδ	III	Hot temperatures (>45°C)
Cold nociceptors	C	IV	Cold temperatures (<5°C)
Nociceptors			Pain
Mechanical	Aδ	III	Sharp, pricking pain
Thermal-mechanical	Aδ	III	Burning pain
Thermal-mechanical	C	IV	Freezing pain
Polymodal	C	IV	Slow, burning pain
Muscle and skeletal mechanoreceptors			Limb proprioception
Muscle spindle primary	Aα	Ia	Muscle length and speed
Muscle spindle secondary	Aβ	II	Muscle stretch
Golgi tendon organ	Aα	Ib	Muscle contraction
Joint capsule mechanoreceptors	Aβ	II	Joint angle
Stretch-sensitive free endings	Aδ	III	Excess stretch or force

Figure 8: Receptor types in somatic sensation. (Kandel E, Schwartz J and Jessel T (2014). Principles of Neural Science. New York, Elsevier).

Because motor and sensory axons run in the same nerves, disorders of peripheral nerves (neuropathies) usually affect both motor and sensory functions. Some patients with peripheral

neuropathy report abnormal paresthesias, having impaired perception of cutaneous sensations (pain, temperature) because the small myelinated fibres that carry these sensations are selectively affected; instead, the sense of touch may or may not be involved. In the same manner, proprioceptive sensation (position and vibration) may be lost without loss of cutaneous sensations [1].

At first, a loss and demyelination of the thin nervous terminations can be observed accompanied by a reduction of the nerve conduction velocity (NCV); muscular atrophy, muscular weakness and autonomic dysfunction manifests at the end of the pathology subsequent to the damage of larger diameter fibres [86-91]. The nervous degeneration starts from the foot, rich in proprioceptors (muscle spindles) and superficial and deep pressoceptors, and goes on to affect more proximal parts of the lower limbs, following a dying back pattern (distal–proximal direction), which is characteristic of failure in fast axonal transport [77, 78]. Damage at the mechanoceptors (i.e., Pacinian and Meissner corpuscles), which convey information about vibration perception in large-diameter myelinated peripheral axons through the dorsal column spinal pathway, leads to a characteristic elevated vibration perception threshold (VPT) [51]. The reduced "length constant" of large diameter axons due to altered cross-sectional volume (i.e., early stages of a dystal axonopathy) seems to be the main cause that contributes to slowed down nerve conduction velocity (NCV). This early structural pathology could reasonably be due to a diminished production of endoskeletal and growth-associated proteins.

This multi-composite pathological picture affects almost all simple movements or activities which require a sensorimotor integration process [92, 93], such as walking, running, driving or simply maintaining balance in a static and dynamic condition. Increasingly, scientific evidence reports that peripheral diabetic neuropathy is one of the main cause of postural instability, uncoordinated gait and related fall injuries [94-96].

5 AIMS OF THE STUDY

Most people do not find difficulty in performing daily activities such as maintaining stance, walking, running or driving because visual motion information helps for navigation in the environment as it carries information about the location, orientation and movement of our body (self-motion) [97, 98]. The synergistic input from the visual system, vestibular-proprioceptive postural reflexes and the nervous system make corrections so that we can maintain a more stable upright posture and perform such activities which require continuous feedback [99]. However, little is known about how somatosensory information is processed and combined to generate appropriate motor responses when there is conflicting or inaccurate orientation information from different sensory systems (sensory reweighting process) [23, 100, 101]. Each specific condition relies on behavioural patterns that can be revealed by clinical sensory organization tests referred as "visual preference", "somatosensory dependent" (also called "visual and vestibular dysfunction"), or "vision dependent" i.e they are dependent on the somatosensory information available in that system, and for such specific pathological conditions [20]. In diabetes, complications such as diabetic retinopathy (DR) and diabetic peripheral neuropathy (DPN) alter visual information and somatosensory inputs, becoming one of the more striking causes in impairing sensorimotor integration process [91, 102].

Diabetic retinopathy (DR) disrupts visual function, as a consequence of microvascular complications which lead to retina degeneration [61]. The proliferative form of diabetic retinopathy requires specific clinical laser treatment, which provokes a loss of visual receptor in the peripheral portion of the retina. Laser scars expansion may be associated with further photoreceptor loss, retinal pigment epithelial hypertrophy, and functional loss [103]. Several self-administered questionnaires investigate the relationship between visual function parameters (visual acuity, contrast sensitivity, colour vision) and quality of life represented by normal activity such as "going

out" or "reading" and they found that the reduction of the visual function negatively correlates with the disability index related to daily life activity [70]. Diabetic people with and without neuropathy (DPN) present a deficit and/or a lack in various sensory information processing to the postural system [1], a condition which predisposes this population to a 15 times greater risk of a fall when compared to age-matched healthy adults [104, 105]. The reduction or the lack of proprioceptive and tactile inputs and/or motor output (reaction time and strength), caused by diabetic peripheral neuropathy [106], lead to abnormal neuromuscular response and to postural disturbance which increases whole body reaction times and postural sway [107].

My PhD research project focused on the evaluation of both central and peripheral nervous factors that contribute to the impairment of the sensorimotor integration process observed in people with diabetes. The evaluation of people with diabetic retinopathy, diabetic peripheral neuropathy and aged-matched healthy controls allow us to quantify and discriminate the different contributions of the visual perception and the somatic sense in daily life tasks, such as during quiet stance or during driving. Results of the motor output in terms of movement pattern and/or muscular responses can give us information about the importance and/or the impairment of each sensory system in a specific physiopathological condition.

This approach could provide a basis for understanding how the nervous system might transform raw sensory signals into internal estimates of body motion and spatial orientation in order to realize an effective and efficient motor output that could be transferred into everyday life tasks [101, 108]. It would be useful to consider models of self-motion perception in different everyday contexts with the purpose of understanding how stimuli at the body's surface are converted by the brain into sensation and planned actions [108, 109].

For these reasons, this research study has been divided in two main parts with the purpose of **evaluating the direct link between visual perception and related motor output responses in**

different conditions of simulated reality: during an optic flow stimulation which induce a perception of forward movement or during a driving task using a simulator.

The aim of the **Study I,** performed at the Department of Biomedical and Neuromotor sciences of the University of Bologna**,** was to assess how optic flow processing contributes to the control of posture and whether it requires the predominant activation of cortical feedforward networks or the intervention of subcortical loops. We sought to investigate the contribution of different directions and dimension of optic flow stimuli that control visuo-postural dynamics in the presence of different retinal functionality. In fact, as a consequence of diabetic retinopathy, different visual perception conditions could directly influence the neural pathways involved in the control of balance and consequently the postural strategies adopted. Using centre-of-pressure measures to assess postural control during quiet standing, several studies have demonstrated that people with diabetes, with and without peripheral neuropathy, reported an abnormal postural control [110-113] and COP area displacement reflecting the severity of the diabetes complications. [114, 115]. Recently, the research field has focused on muscle activation during visual stimulation (comparing eye open to eye closed conditions), and results showed that people with diabetes experienced a wider COP displacement when compared to healthy control in both conditions [115-117]. The unsteadiness experienced by people with diabetes is predominately attributed to the impairment of the somatic and neuromuscular information caused by diabetic peripheral neuropathy [51, 96, 110, 118]. The innovation of this research project was to **evaluate the contribution of the visual perception in people at different stages of diabetic retinopathy**. We assessed the role of different optic flow stimuli directions and dimensions on the postural muscles (anterior tibialis and soleus), directly linking the muscle activity to the evoked oscillation measured by changes in the centre of pressure (COP). The observation of the combined stabilometric and electromyographic data would shed light on the neural pathway involved in the control of

neuromuscular response to specific visual field characteristics and retinal functionality. Results of this neurophysiologic study could be useful in order to create specific programmes directed at the functional rehabilitation of the postural system in this population.

The aim of the **Study II,** performed at the School of Health Care Science of the Manchester Metropolitan University, was to assess whether diabetes was associated with alterations of visual gaze behaviour and/or neuromuscular impairment that might adversely affect driving performan**c**e. Given the importance of eye movements to optimal and safe driving [119-121], we sought to evaluate eye-steering coordination during driving in diabetic people with and without diabetic peripheral neuropathy (DPN). Recent studies have demonstrated that lower extremity sensorimotor neuropathy patients had slower mean brake response times and have an increased frequency of abnormally delayed brake reactions compared with diabetic without neuropathy and healthy control [122, 123]. Based on these findings, **we hypothesized that this population might have at least the potential for impaired driving function.** Even though the detrimental effects of diabetic neuropathy on gaze, muscle strength, gait and balance performance have been widely demonstrated [124-127], to our knowledge there have not been any previous studies designed to investigate possible relationships between these factors. Besides the evaluation of the oculomanual coordination (eye-steering coordination) we wanted to compare motor reactions of the plantar flexor muscles and control of the foot with the use of the pedal during driving. Until now, the risk for driving in the diabetic population has been associated to visual impairment [72] and/or the risk of hypoglycaemic events during driving [128]. The innovation of this research project was to evaluate the driving task, as regards the posture, in an action perception paradigm, in which the comparison of multiple data (usually taken separately), was used in order to find a clearer connection between visual perception and associated motor pattern movements in order to quantify the contribution of each sensory system. This integrated approach forms the primary aim of this study and is an important question to address for two reasons: 1) from the point of view of working towards an

objective test of fitness to drive and 2) since we know the importance of visual gaze behaviour for safe driving performance. In terms of the first issue, fitness to drive is currently a subjective judgement made by a general practitioner, whereas this study would work towards making this an objective measure. In terms of the second issue, aware of the fact that visual gaze behaviour during walking can be improved through training [129], we hypothesized that it could be the same for driving; thus we would anticipate being able to improve driving performance through eye-movement training. Visual gaze training to improve driving performance would be an intended future application of this initial research study.

6 STUDY I

The first part of my research project entitled “The postural stability in the diabetic retinopathy: stabilometric and electromyographic study” was supervised by Professor Milena Raffi, Professor of Human Physiology at the Department of Biomedical and Neuromotor Sciences of the University of Bologna. Recruitment of subjects with diabetic retinopathy was done by an ophthalmologist, Professor Sergio Zaccaria Scalinci, based on research at the University of Bologna. Healthy control subjects were recruited within personnel of the University of Bologna. All experiments were conducted in the laboratory of Neurophysiology at the University Centre "Record” of the Department of Biomedical and Neuromotor sciences of the University of Bologna.

6.1 INTRODUCTION: THE FUNCTIONAL IMPORTANCE OF OPTIC FLOW

Vision plays an essential role in the multisensory control of postural balance [98]. More than 20% of the motor cortical cells are modulated by optic flow stimuli. We can assume that visual motion information (optic flow) represents a robust input to motor cortex [24, 28, 30]. It seems that the visual system analyses the visual component “optic flow” first, and then it combines its characteristics with the other retinal and extra-retinal signals in order to construct dynamic maps of extra-personal space suitable for self-motion guidance and postural stabilization [30]. Three major sensory systems are involved in the postural system; visual, vestibular and somatosensory. Vision is the system primarily involved in planning our locomotion and in avoiding obstacles along the way. The vestibular system senses linear and angular accelerations and the somatosensory system is represented by a multitude of receptors that sense the position and velocity of all body segments, their contact (impact) with external objects (including the ground), and the orientation of gravity [130]. On the basis of the integration of these systems, posture can be defined as the relative position of the various part of the body with respect to one another (the egocentric coordinate

system) and to the environment (the exocentric coordinate system) plus a third frame of reference regarding the gravitational field (the geocentric coordinate system) [131].

Several studies have investigated the influence of the visual input on the postural stabilization in healthy subjects [4, 9, 11, 132]. Other studies have observed the changes of the COP sway in response to different visual stimulation [21, 133, 134] but the main finding was that by using visual feedback (eyes open), subjects with normal vision can reduce postural sway by about 50% compared to non-use of it (eyes closed) [6, 9, 135-137].

Moving visual scenes can elicit postural responses [137-139]; on the other hand, in spite of the sway response produced by moving visual stimuli, the oscillation speed is generally lower in the presence of a visual stimulus compared to the absence of it [137]. Lee et al. for the first time demonstrated how the manipulation of optic flow affects postural stability [140]. They developed the "swinging room paradigm" that allow the visual environment to be manipulated in a controlled manner in order to produce a convincing sense of self-motion for the observer. They found that body sway was manipulated by the movement of the room in which the subjects stood [137]. Other results showed that adults increased antero-posterior oscillations which were in phase with the room when the misleading visual information was presented [139]. At the same time, recent studies affirmed that the specific inter-leg coordination dynamics necessary to maintain the control of posture during optic flow stimulation were the direct consequence of a foot asymmetry in the function of controlling balance [141]. These findings might suggest that the postural control system uses various mechanisms within each leg to produce the most appropriate postural response to interact with the extra-personal environment.

Despite the fact that visual stimuli seem always to evoke an excitatory input on postural muscles, the stimulus structures produce different postural effects. Peripheral optic flow stimuli stabilize postural sway, while random and foveal optic flow provoke larger sway variability similar

to those provoked in the absence of visual stimulation [141]. Taking into account the functional importance of these stimuli in relation to the portion of the retina in which they are processed, peripheral vision seems to have a fundamental role in postural stabilization, while fovea could have a fundamental role in heading direction [142].

6.1.1 EFFECTS OF DIMENSION OF OPTIC FLOW VISUAL FIELD

Foveal and peripheral vision can be distinguished depending on their structure and functional processing characteristics [142]. Foveal and para-foveal vision occupy about 50% of the primary visual cortex while the rest of the visual field needs to share the residual half of the cortical representation. Visual field of the same size but different retinal locations differ quantitatively, because cortical representation decreases with increased eccentricity [143]. Thus, a peripheral field has a much smaller cortical representation than a central field. Separate functional specializations of central and peripheral retina for balance control suggest differential effects on visual stabilization of sway. When a perceiver moves forward in the world (or stands in a moving room), the optical flow that is generated does not have the same geometrical structure everywhere [27]. We could observe several properties of motion perception in the periphery of the visual field: horizontal motion is detected better than vertical motion and generally, centrifugal movements are more readily detected than centripetal movements. The superiority of the centrifugal motion detection might mirror an adaptation of the visual system to the foveo-fugal patterns that are continuously experienced during locomotion or forward movement experience. When we move forward, the retinal projection of all peripheral objects usually move centrifugally due to an increase in their retinal projections with decreasing distance. This directional asymmetry of stimulation might lead to a modification of the directional selectivity of cortical neurons [144]. This evidence suggested the importance of the fovea and periphery in the pickup of optical information as a function of the dynamic structure of the optical flow [15]. The retinal periphery essentially seems to be an organ for recording and

controlling the position and motion of the perceiver’s head relative to the environment, thus locomotion of self-motion; while the fovea detects the direction of the movements.

When moving forward, the flow near the line of motion expands in front of the observer, but at the edges of the field of view flow sweeps laterally past the observer. Between the centre of radial expansion and the edges of the field there is a continuous change from expanding to lamellar flow, resembling the change in structure of longitudinal lines from a pole (radial) to the equator (lamellar). When the eyes look in the direction of the movement, predominantly radial flow is projected to the central regions of the retina, whereas in the periphery the lines of flow have a lamellar structure. However, if the observer were to turn to face the side of the room, this relationship would be reversed: lamellar flow would fall on the retinal centre and radial flow in the periphery. We can imagine that a determinate structure of the visual flow is responsible to engage sets of motor cortical cells in response to different visual stimulation that makes every single cortical area differently excitable [143-146].

Retinal regions are differently sensitive to the translational (lamellar) and rotational (radial) flows. The fovea is more sensitive to the radial flow, the periphery is more sensitive to the lamellar flow [145]. It thus seems that the peripheral dominance approach to the optical control of stance is correct, but a more ecologically oriented approach, such as Gibson's is also correct. One must takes into account not only the function of the receptor organ but also the structure of the information in the ambient optic array [147].

Many theories state functional differences in the contribution of central and peripheral vision [148]. The first theory states that peripheral vision plays a major role in the control of stance [142], while the second states that there are no functional differences between central and peripheral vision in the control of posture [143]. The third suggests that both are necessary and complementary. [16, 39, 149, 150]. The final assessment of retina based theories in light is not entirely straightforward.

The main reason of such discordances are the different experimental protocols used in those studies. Different definitions of fovea and periphery, and different method and stimuli characteristics (velocity, motion) imply different retina representation and consequently different responses [151]. There is a difference in sensitivity between different areas of the retina, but it is more complex than had previously been supposed. [152]. In conclusion, it seems that central retina has a modest capacity to use radial and lamellar flow for the control of stance. On the other hand, the peripheral retina appears to be specialized to the pickup of information for postural control from flow having lamellar geometry, but it is less sensitive to radial flow for controlling posture [145].

6.2 POSTURAL CONTROL ASSESSMENT

One of the most efficient ways of showing how we perceive visual flow is to record the postural reactions of standing subjects. Sway has been viewed as a consequence of noisy processes within the human neuromotor system, as a reflection of an active search process [150], and as an output of a control process of stabilization of an unstable structure, human body [153]. At the same time, the human body was compared to an inverted pendulum model in order to explore how the central nervous system controls balance [46, 154] (Fig. 9).

Stabilometry is a technique used to study the body sway during quiet standing, i.e., stance in the absence of any voluntary movements. Conventionally, the study focuses on the properties of body sway during upright standing, thus far primarily measured by means of force plates in order to evaluate the Centre of Pressure (COP) displacement. COP is the point location of the vertical ground reaction force vector; it represents the weighted average of all the pressures over the surface of the area in contact with the ground. If one foot is on the ground the COP lies within that foot. If both feet are in contact with the ground the net COP lies between the two feet, depending on the relative weight taken by each foot. Thus, when both feet are in contact there are separate COPs under each foot. The location of the COP under each foot is a direct reflection of the neural control

of the ankle muscles. The different patterns of muscle activation reflect the response to changes in COP position and analysis of the EMG signals becomes useful for understanding the muscle strategy used for stabilizing posture. As an indicator of the initiation of muscle activity, the EMG signal can provide the timing sequence of one or more muscles performing a task, such as during gait or in the maintenance of erect posture [131].

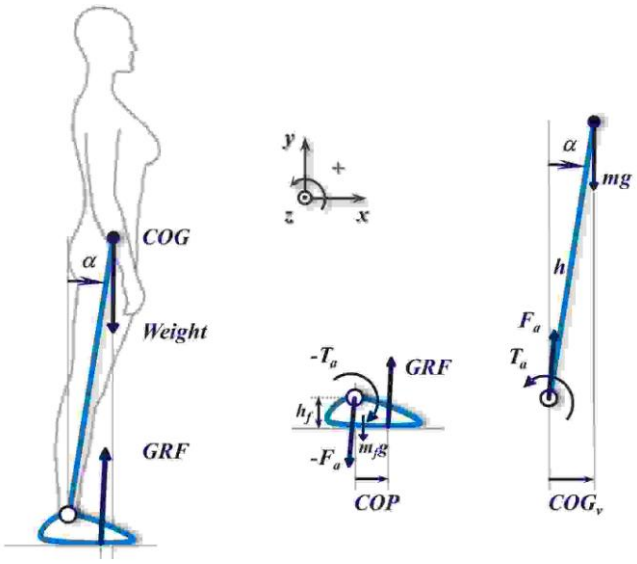


Figure 9: Model of a two-link human inverted pendulum and the external forces acting on it in the sagittal plane and the corresponding free-body diagrams. COG: body centre of gravity; COG_v: COG vertical projection (horizontal plane) in relation to the ankle joint; COP: centre of pressure in relation to the ankle joint; GRF: ground reaction force (from a force platform); α: angle of the body in relation to the vertical direction; m: mass of the body minus feet; g: gravity acceleration; Fa: resultant force at the ankle joint; Ta: torque at the ankle joint; h: height of the COG in relation to the ankle joint; mf: mass of the feet and hf: height of the feet .

The use of surface electromyography (EMG) combined with stabilometry may offer important information about the muscles' behaviour when submitted to the many different types of overload, many angles and performance velocities; as well as the evaluation of the myoelectrical behaviour in many circumstances. The EMG signal reflects electrical activation of muscle fibres [155, 156]. Muscular contractions are the basis of coordinated movements and all skeletal muscle activity is controlled via the motor nervous system. Electromyography provides information about the muscle

function through the observation of the electrical signal which comes from the muscle, also being essentially the study of the activity of the motor unit [156]. As an indicator of the initiation of muscle activity, the signal can provide the timing sequence of one or more muscles performing a task, such as during gait or in the maintenance of erect posture. Another important application of the EMG signal is to provide information about the force contribution of individual muscles as well as groups of muscles.

Postural muscles are located at different sites in the human body, including lower body muscles such as calf muscles (tibialis anterior, soleus and gastrocnemius) and thigh muscles (hamstring, quadriceps femoris, tensor fascia lata) playing fundamental roles in balance control as they oppose the destabilizing effects of gravity [157]. Small disturbances mainly evoke compensatory movements in the ankle joints (ankle strategy) [158, 159]. On the other hand, when the ankle joint torque becomes insufficient, more proximal muscles (hip strategy) intervene; hip joint accelerations produce shear forces under the feet able to counteract body centre of mass excursions (that is the point on a body that moves in the same way that a particle subject to the same external forces would move) [158, 159]. Nasher et al. described the ankle strategy as early activation of dorsal ankle muscles followed by activation of dorsal thigh and trunk muscles while the hip strategy was recognizable as an early activation of ventral trunk and thigh muscles [131]. During moderate disturbances, another aspect of hip–ankle coordination needs to be considered. In such situations, while the ankle joints perform the primary task to maintain equilibrium of the whole body [8, 160]; the hip joints tend to perform a secondary task, consisting of the stabilization of the vertical orientation of trunk and head and thereby stabilizing the workspaces of the hands and for the eyes [161]. This postural response enables the reduction of head movements during body oscillations (i.e., head stabilization in space strategy), and it is thought to improve sensory feedback from the vestibular and visual cues during dynamic balancing [162-164].

6.3 AIMS OF STUDY I

Since the classic experiments of Witkin and Wapner in the 1950s, later extended by Lishman and Lee (1973), Lee and Aronson (1974), Lee and Lishman (1975) and Lestienne et al. (1976, 1977), systematic and global postural readjustments were evaluated when the optical environment was moved by means of different devices. The stimuli used in research attempt to simulate the characteristics of an optical flow produced by a moving observer during locomotion, allowing evaluation of its functional importance in the control of balance [27]. It Is well known that vision plays a major role in the control of posture due to the differential contributions of the foveal and the peripheral region of the retina in the perceptual process [142]. Such functional differences seem to be mainly due to the characteristics of the stimuli [27]. So, the question that arises is whether the different effects in visual stabilization of sway reflect a separate specialization of central and peripheral retina, and what happens in the presence of different retinal functionality.

The self-motion perception produced by optic flow fields is part of the sensorimotor integration process designed to stabilized posture in both static and dynamic condition. What is more, when comparing several visual disability indexes for the diabetic retinopathy population, we found the visual index for “going out” correlated with contrast sensitivity and peripheral visual field in people with diabetic retinopathy [70] and we could infer that the perception of the observer while moving might be impaired in this population.

The majority of the research studies focused on the maintenance of balance control, looking at the COP variation trajectory using the static and dynamic posturography paradigms, recording the spontaneous postural oscillation in an eyes-open or eyes-closed condition or in response to specific external perturbations [165, 166]. The aim of the present study was to evaluate the role of optic flow stimuli with different directions and dimensions on the postural muscles, directly linking the muscle activity to the evoked oscillation measured by COP changes. We induced a perception of

movement in a static condition using an optic flow stimulus consisting of radial expansion dots, which stimulated the foveal, peripheral and full visual field while simultaneously recording the COP displacement and the pattern of muscular activity of the anterior tibialis and soleus. Recordings were performed in both diabetic subjects with retinopathy and healthy people. Specifically, the experiments have been carried out on diabetic people at an early stage of retinopathy and on diabetic people who had a laser treatment on the peripheral part of the retina. We quantitatively evaluated the body sway and the corresponding muscle pattern recruitment in order to have more information on the underlying neural circuit (feedback or feed-forward) activated in response to such stimuli conditions. The same experimental conditions were presented to age-matched healthy control group in order to assess if any differences between groups exist, but especially to better understand and differentiate the negative effects, and identify whether they are due to the aging process or due to the pathological condition.

The innovative part of this research project was to evaluate the contribution of visual perception processes in people who show retinal deficits without the conscious experience of an altered perception. Evaluating people with different retinal damage, in terms of severity and location, could highlight specific patterns of movements and muscles recruitment corresponding to specific perception condition. The analysis of the optic flow stimulation in different portions of the retina with different retinal lesion locations will allow to understand the contribution of the foveal and peripheral regions of the retina in maintaining balance.

Postural control requires a combination of feedforward and feedback neural mechanisms (i.e., production of movements or muscular contractions) that help keep the body upright in space. In addition, the feedback mechanisms involve movements of the head through the vestibular system in the inner ear, visual feedback, and feedback about pressure changes through the support surfaces of the body [1]. The feedforward mechanisms include signals that are able to anticipate disturbances to

the postural control system that will arise as a consequence of movement [167]. However, the organization of these feedback-control mechanisms is still unknown, as is whether these mechanisms play a dominant or a minor role in postural control. Studies reported that feedback control alone is insufficient to explain human postural control [168]. Few studies have shown that moving visual fields can induce a power sense of self-motion, and when visual input is ambiguous, we can observe an increase in body sway that correspond an active search process by the neuromotor regulation system [169-171]. Few studies investigated the complex task that requires the maintenance of postural stability to elucidate the relative contributions of each sensory system during standing, suggesting that visual feedback differentially influences the neural control of body sway in males and females. Neural activity seems to provide the motor system with different afferent inputs in response to disturbances of the body balance [172].

We sought to understand the underlying mechanisms, which control the postural system starting from the visual perception process. We aimed to assess how optic flow processing contributes to the control of posture and wheter it requires the predominant activation of cortical networks involved in motion perception or the intervention of subcortical loops.

6.4 RESEARCH DESIGN AND METHODS

6.4.1 PARTICIPANTS

Thirteen people in the early stage of retinopathy (Retinopathy group, average age 63 ± 12), eight people with a laser treatment on the peripheral retina (Laser group, average age 56 ± 15), and thirteen healthy subjects (Control group, average age 59 ± 9) gave their written consent to take part in this study. The experimental protocol was approved by the Bioethics Committee of the University of Bologna (Italy). The experiments were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Major exclusion criteria were the assumption of any drug that could have an effect on the central nervous system, the presence of any

musculoskeletal problem and /or major complication of diabetes that could affect the balance and consequently postural control. The hand and foot laterality of each subject was assessed by a laterality questionnaire [173, 174] before the beginning of the experiment using the following formula:

[(right preference – left preference)/(right preference + left preference)] x 100

A positive laterality index was indicative of a right dominance, while a negative index was indicative of a left dominance.

6.4.2 DIABETIC RETINOPATHY ASSESSMENT

Participants were divided into the two groups based on the ophthalmoscopic measurement operated by a clinician. Retinopathy assessment was made by fundus oculi photography. A single-field fundus photography interpreted by trained readers (only one photograph is required) is the most easy and convenient method to detect retinopathy [65]. People with non-proliferative retinopathy and presenting only a few micro-aneurysms were assigned to the “Retinopathy group”. People with proliferative retinopathy who had already undergone laser photocoagulation treatment in the peripheral retina were included in the laser treated group “Laser group”. “Control group” was formed by people with normal retinal functionality. All participants underwent a visual acuity test and visual field test [66].

6.4.3 APPARATUS

STABILOMETRY AND SURFACE ELECTROMYOGRAPHY

The data acquisition protocol was similar to that reported in a previous paper [175]. The task consists of recording stabilometry and electromiografic data simultaneously while subjects had to fixate the central fixation point (FOE) and optic flow stimuli were retroprojected on a screen (Fig.10). They did not receive any instructions to resist the motion perception evoked. Trial onset

determined the stimulus onset. All the subjects performed at least four trials of normal standing of about 30 seconds. Optic flow registrations were all performed in a dark room.

Stabilometric data were recorded using two Kistler® force platforms (Kistler Instrument Corp. NY, USA) placed side by side. Subjects were instructed to place a foot on each platform with both arms along the trunk.

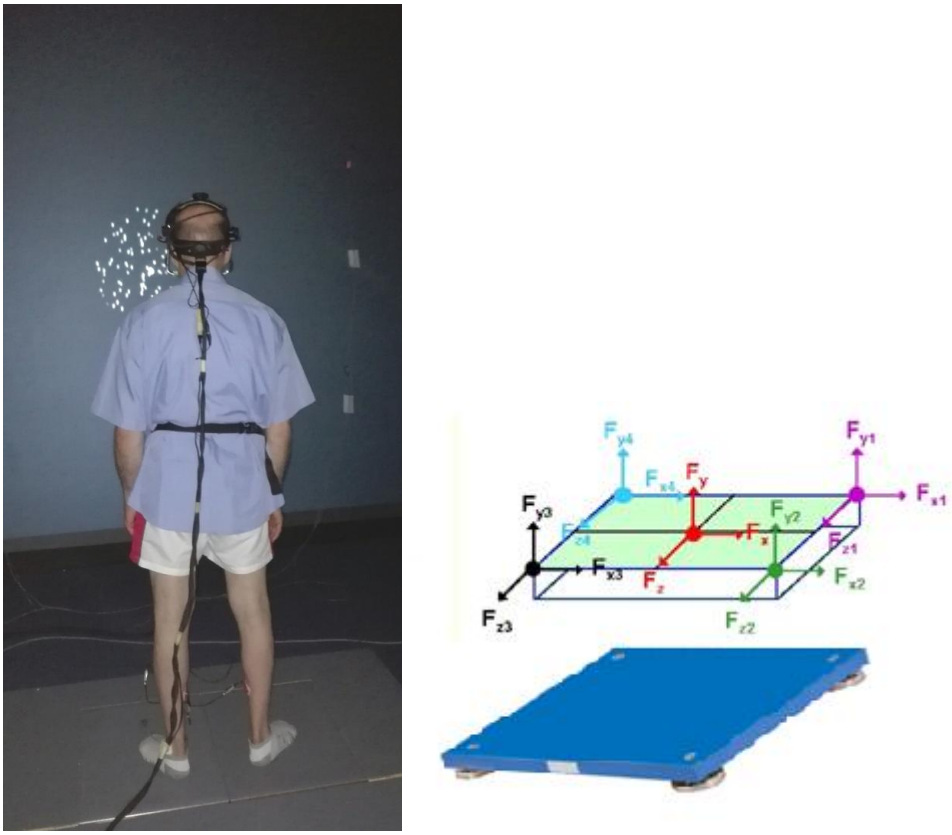


Figure 10: The experimental set-up was provided with two force platforms (Kistler®) with four load force sensors. The figure on the right shows a Kistler force platform and a model which represents the three force components, Fx, Fy and Fz (x, y, and z) which act on the platform. Participants had to stand still and place a foot on each stabilometric platform positioned in front of a screen (135 × 107°) on which stimuli (foveal, in this case) were retro-projected. Electromyographic data of the tibialis anterior and soleus muscles of both legs were recorded using a pocket sEMG (BTS Bioengineering Inc.®) that was tied at the waist. An eye movement tracking system (EyeLink II®), mounted on a headband, was used to collect visual focus of expansion (FOE) fixations.

Stabilometry is the measurement of forces exerted against the ground from a force platform during quiet stance; it allows to obtain, indirectly, an assessment of changes in postural oscillation in order to provide quantitative measures of postural sway [176]. In general, the force plate is a

laboratory tool consisting of a board in which some (usually four) force sensors of load cell type or piezoelectric are distributed to measure the three force components, Fx, Fy and Fz (x, y, and z are the anterior-posterior, medial-lateral, and vertical directions, respectively), and the three components of the moment of force (or torque), Mx, My, and Mz, acting on the plate. Typically, stabilometry focuses on the properties of the COP time series, representing the point location of the ground reaction force vector as it evolves on the horizontal plane (2D) or along two orthogonal axes, fixed with the platform (antero-posterior and medio-lateral) [177]. The COP in both anterior-posterior and medial-lateral planes has proven to be a significant and reliable output metric [178].

At the same time, EMG data were acquired by a 16 channel Pocket EMG BTS (BTS Bioengineering Inc.) using Ag/AgCl disposable electrodes 32 x 32 mm (RAM Apparecchi Medicali s.r.l.). Electrodes had an active area of 0.8 cm^2 with an inter-electrode distance of about 2 cm. At the beginning of the experiment, subjects were prepared for the electromyographic recordings. The skin was shaved and cleaned with ethanol before placing the electrodes to improve the contact with the skin. Electrodes were positioned on the muscular belly of the following muscles: left tibialis anterior (LTA), right tibialis anterior (RTA), left soleus (LSOL), right soleus (RSOL). The reference electrode was placed on the malleolus bone (electrically neutral tissue). After placing the electrodes, we acquired the maximum voluntary contraction (MVC) of each muscle using isometric machines. The peak of the MCV was used for the normalization of EMG activity. Surface EMG was acquired by using electrodes lightweight and small placed directly on the skin over the desired muscle of interest, allowing subjects to move freely [179].

EYE TRACKING SYSTEM

The eye position was checked online by an eye tracking system EyeLink II (SR Research Ltd, Mississauga, Canada), used to collect visual search data, and trials with incorrect fixation were discarded. The eye link system uses a corneal-reflection of an infrared light. This allows the

recording of the participant's eye movements on video using a camera mounted on a headband. Since the position of the corneal reflection remains constant relative to the headband but the centre of the pupil moves whenever the eye moves, the system is able to measure the difference between the centre of the pupil and corneal reflection, and from this is determines the position of the eyes. We used three-horizontal-point calibration in order to map raw eye data to gaze position. Before the beginning of each trial participants had to keep the head still and look subsequently at three points on a grid shown in a random order on a black background. Subjects were asked to keep looking for the whole duration of the task and maintain a still head. The fixation point (FOE) projected on the screen was adjusted according to the height of each subject. Each trial consisted of a stimulus period of 30 s. We acquired 5 trials for each stimulus condition.

OPTIC FLOW STIMULI

The stimuli consisted of luminous dots moving coherently to produce optic flow patterns, which simulated specific heading directions. Given that in a previous study we did not find a significant modulatory effect of optic flow direction on muscle activity [175], in the present experiment we only used expanding optic flow.

Optic flow stimuli comprised white dots (1.3 cd/m^2, size 0.4°) were presented full field, in the foveal or in the peripheral region of the visual field by a retro video projector (Sony VPL EX3) positioned 415 cm away from a translucent screen. The screen covered 135 × 107° of visual field and was placed 115 cm from the subjects' eyes. The dots moved on the screen at a speed of 5°/s. All stimuli had the same dot density with respect to the retinal stimulation area. We changed the stimulus dimensions to stimulate different portions of the retina and we manipulated the spatial distribution of dot speed to simulate specific heading directions. Because the speed of the optic flow motion depends on the distance of the FOE from the eye of the observer, objects near to him/her move faster in the retinal projection than the objects further away [3]. The dot speed was

accelerated to the left or to the right visual hemifield to simulate different headings at different angles of gaze [180, 181]. Fixation point (FP) to the centre and dots accelerated to the left simulated heading direction to the left with fixation straight ahead (DirL-FixC,Fig. 11-A). In the full field expansion stimulus, the dots motion originated from the FOE moving radially towards the periphery (DirC-FixC, Fig.11-B). FP to the centre and dots accelerated to the to the centre and dots accelerated to the right simulated heading direction to the right with fixation straight ahead (DirR-FixC, Fig.11-C).

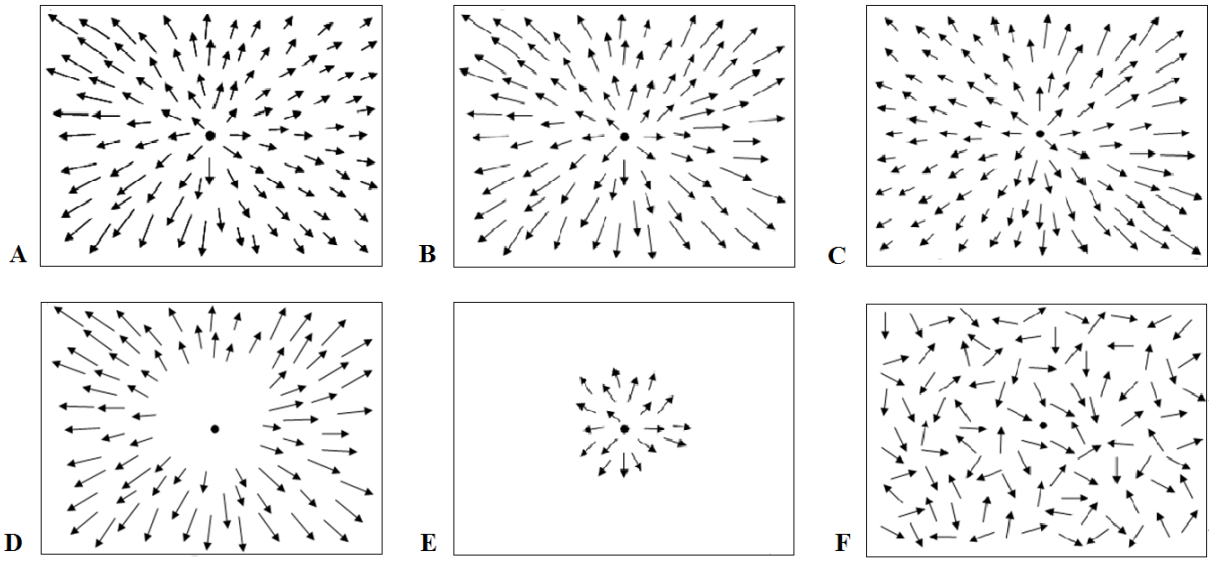


Figure 11: Optic flow stimuli. A. Fixation point (FP) to the centre and dots accelerated to the left simulated heading to the left with fixation straight ahead (DirL-FixC). B. Radial expansion concentric with the FP simulated heading and fixation straight ahead (DirC-FixC). C. FP to the centre and dots accelerated to the right simulated heading to the right with fixation straight ahead (DirR-FixC). D. Peripheral stimulation, the blank area in the centre had a radius of 20°(Periphery). E. Foveal stimulation, the stimulated area had a radius of 7°(Fovea). F. Random dots motion. *Arrows* represent the velocity vectors of moving dots. Optic flow stimuli were made using Matlab psychophysical toolbox (The Mathworks Inc.).

In the methodological preparation of this study, it was decided to follow anatomical criteria [182], so central visual field was considered to be the 7° surrounding the fovea. This includes the foveal, parafoveal and perifoveal regions. Periphery was considered to be the visual field outside the inner 20° of the central visual field so as to be sure to analyse the retinal area containing almost

exclusively rod photoreceptors [183]. Peripheral stimuli covered the entire screen except a central occlusion circle of 20° in radius.

In the peripheral expansion stimulus, the dots originated from the edge of the central black portion of the visual field moving radially towards the periphery (Periphery, Fig.11-D). In the foveal expansion stimulus, the dots originated from the FOE moving radially towards the periphery (Fovea, Fig.11-E). Random dots motion (Fig.11-F) and fixation on a dark screen (Baseline) were used as control stimulus. Optic flow stimuli were made using Matlab psychophysical toolbox (The Mathworks Inc.).

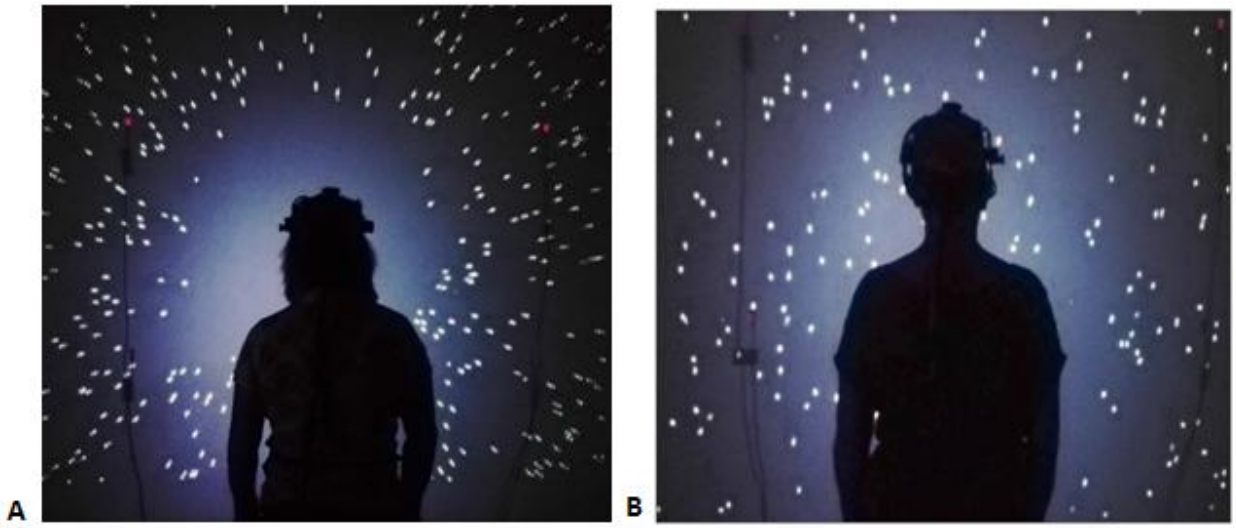


Figure 12: Examples of optic flow presentation. A. Foveal stimulation. B. Full field stimulation.

6.5 DATA ANALYSIS

6.5.1 STABILOMETRY AND SURFACE ELECTROMYOGRAPHY

Both EMG and stabilometric signals were recorded at 1000 Hz. In order to avoid fatigue effect, the first 29 sec of each trial were analysed first. In the initial step of the analysis EMG signals were positively rectified and band pass filtered (Butterworth, 20–450 Hz) using SMART Analyzer (BTS Bioengineering Inc.). Then signals were resampled at 250 Hz and were normalized to the maximum voluntary contraction [184, 185]. The normalized root mean square (RMS) values were calculated in 100 ms bin using Matlab.

Stabilometric data were low-pass filtered at 15 Hz and resampled at 250 Hz. Ground reaction forces and COP measures were recorded from each foot by the two platforms. Both antero-posterior (COP_{AP}) and medio-lateral (COP_{ML}) directions of COPs of each foot were analysed using either SMART Analyzer (BTS Bioengineering Inc.) and Matlab (The MathWorks, Inc). The global COP (COP_{net}) values for mediolateral (COP_{net_ML}), antero-posterior (COP_{net_AP}), area (COP_{net_Area}) and velocity (COP_{net_Speed}) were computed from a weighted average of the two COPs, according to the following formula [186]:

$$COP_{net} = COP_L * R_{VL} / (R_{VL} + R_{VR}) + COP_R * R_{VR} / (R_{VL} + R_{VR})$$

where: R_{VL} and R_{VR} are the vertical reaction forces from left and right feet respectively.

The COP velocity (COP_{Speed}), reflects the total distance travelled by the COP over time on each axis while the COP area (COP_{Area}), quantified within the 95% confidence ellipse, represents the enclosed area covered by the COP as it oscillates within the base of support [130, 187-190].

6.6 STATISTICS

In order to analyse the influence of optic flow stimuli on postural control, a repeated-measures ANOVA of each COP parameters (COP_{AP},COP_{ML}, COP_{Area} and COP_{Speed}) was performed; side (right, left) was the within-subjects factors, while optic flow stimuli (DirL-FixC, DirC-FixC, DirR-FixC, Fovea, Periphery, Random, Baseline) and groups (Laser, Retinopathy, Control) were the between-subjects factors. A univariate ANOVA was used to assess differences between groups (Laser, Retinopathy, Control) in COP_{net} variables (COP_{net_ML}, COP_{net_AP}, COP_{net_Area}, COP_{net_Speed}) while optic flow stimuli (DirL-FixC, DirC-FixC, DirR-FixC, Fovea, Periphery, Random, Baseline) were used as between factors.

A repeated measure ANOVA, in which muscles (anterior tibalis and soleus) and sides (right, left) were set as within factors and groups (Laser, Retinopathy, Control) and stimuli (DirL-FixC, DirC-FixC, DirR-FixC, Fovea, Periphery, Random, Baseline) as between-subjects factors, was used to assess differences between muscle and side (left tibialis "LTA" and right tibialis "RTA") (left "LSOL" and right soleus "RSOL").

Bonferroni post-hoc tests were used to assess differences between groups. All statistical tests were analysed on SPSS statistical package (version 22, Chicago, IL, USA) with significance set at $p<0.05$.

6.7 RESULTS

Answers to the laterality questionnaire resulted in values ranging from "42.86 to 100". Twenty-two subjects out of thirty-three showed a laterality index of 100 meaning that they were completely right-handed. Ten subjects showed values in the range between "80-100" indicating a strong right laterality in all three body segments, and only two subjects presented values between "40-60". No subject turned out to be completely left-oriented.

6.7.1 STABILOMETRY

The results of the repeated measures ANOVA (see Methods) revealed a significant main effect for "Group" in all COP parameters: COP_{ML} ($F_{2,231}$ = 19.26, p<0.001, ηp^2= 0.14), COP_{AP} ($F_{2,231}$ = 32.71, p<0.001, ηp^2= 0.22), COP_{Area} ($F_{2,231}$ = 22.77, p<0.001, ηp^2= 0.16) and COP_{Speed} ($F_{2,231}$ = 20.54, p<0.001, ηp^2= 0.15) (Fig. 13). Bonferroni post-hoc test showed that the Retinopathy group and the Laser group presented the highest value of body sway in the medio-lateral (COP_{ML}) direction compared to the Control group (p<0.001) (Fig. 13-A). All groups were different to each other regarding COP_{AP} (Fig. 13-B), COP_{Area} (Fig. 13-C) and COP_{Speed} (Fig. 13-D).

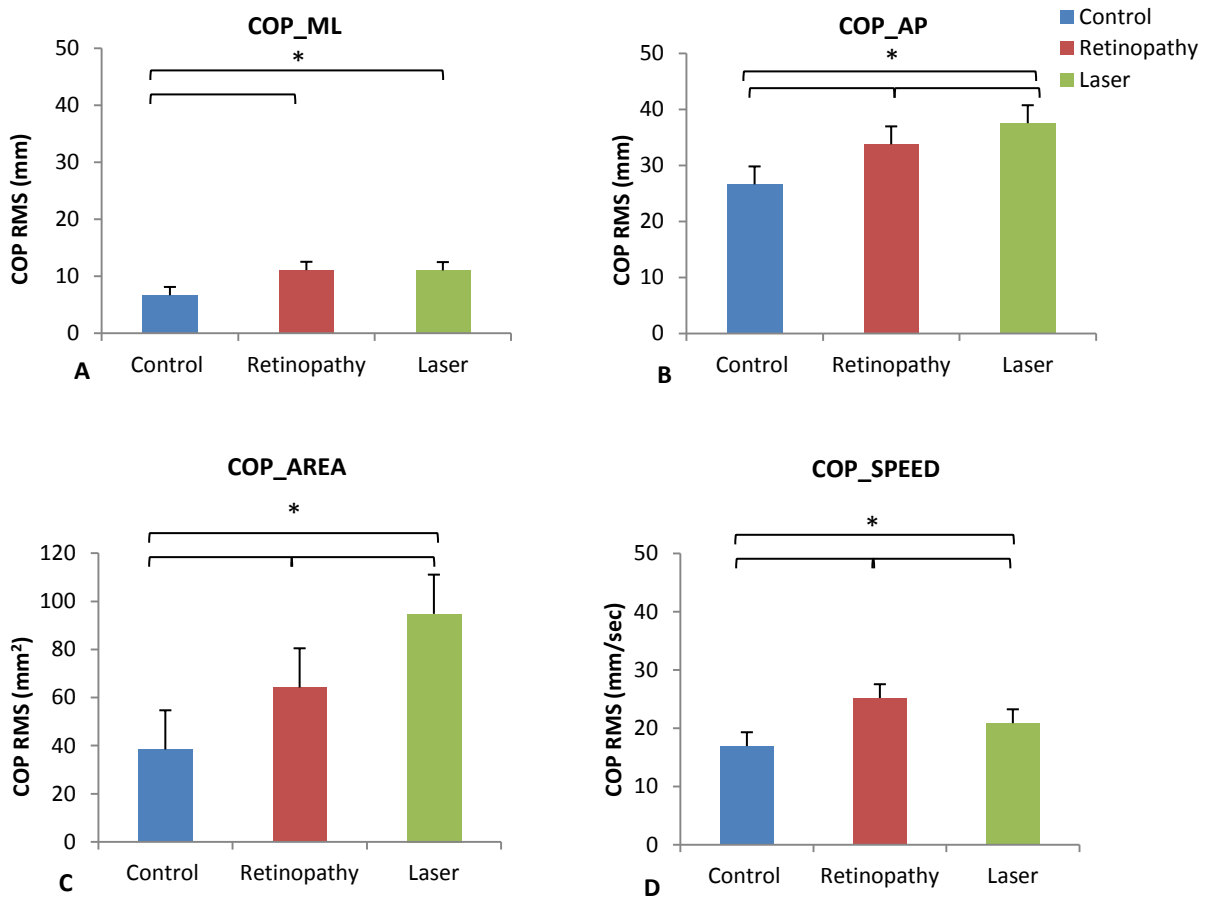


Figure 13: Histograms represent the differences between groups Control (blu bars), Retinopathy (red bars) and Laser (green bars) in COP_ML (A); COP_AP (B); COP_AREA (C); COP_SPEED (D). Asterisks show significant differences (p<0.05).

The laser group showed the highest values in COP_{AP} compared to the Retinopathy ($p=0.34$) and Control ($p<0.001$) groups, at the same time the Retinopathy group oscillated more than the Control group ($p<0.001$). COP_{Area} sway was significantly higher in the Laser group compared to the Retinopathy ($p=0.001$) and the Control ($p<0.001$) groups. At the same time, the Retinopathy group showed higher values compared to Control group ($p=0.001$).

A "Side" main effect was found for COP_{ML} ($F_{1,231} = 12.76$, $p<0.001$, $\eta p^2 = 0.05$), COP_{Area} ($F_{1,231} = 5.30$, $p=0.022$, $\eta p^2 = 0.02$) and COP_{Speed} ($F_{1,231} = 7.10$, $p=0.008$, $\eta p^2 = 0.03$). COP_{ML} sway was wider in the right side (Fig. 14-A) while the values of COP_{Area} (Fig. 14-C) and COP_{Speed} (Fig. 14-D) were significantly higher in the left side.

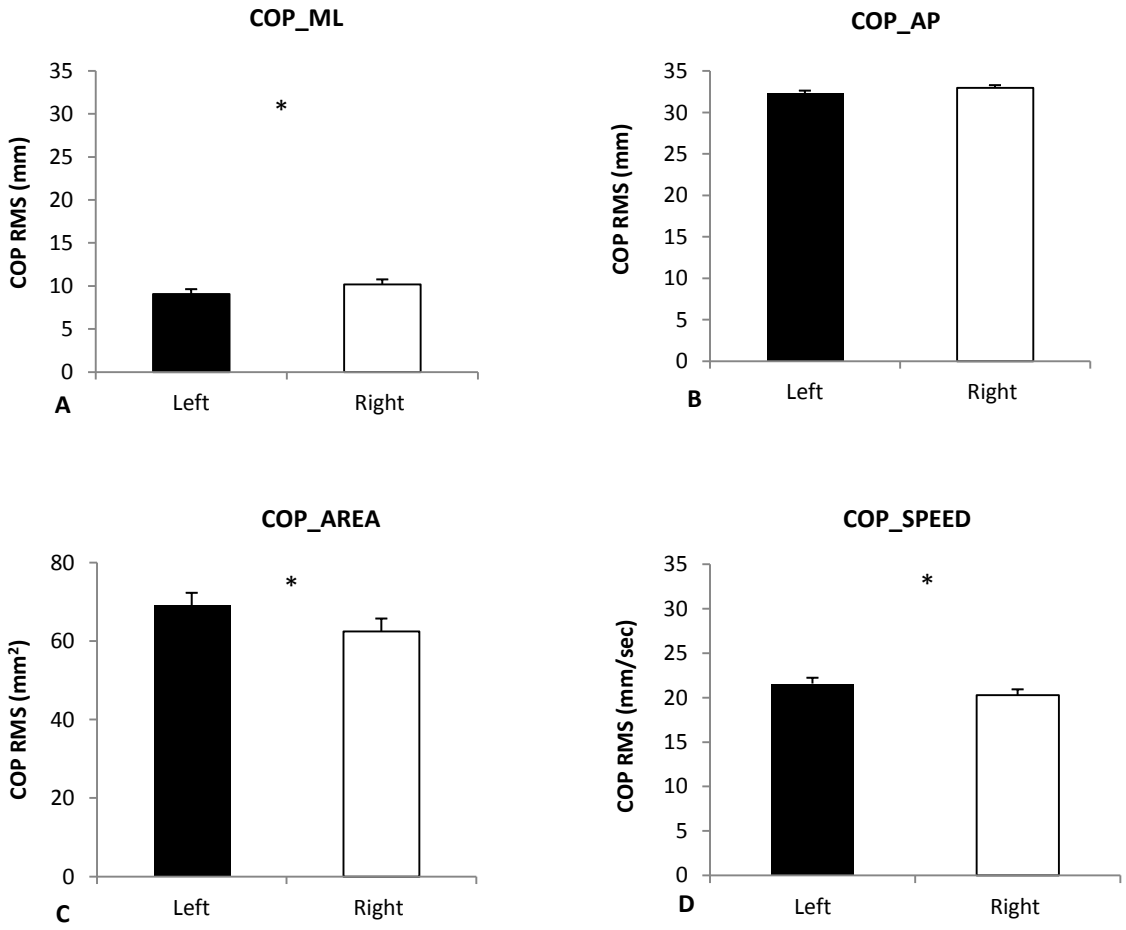


Figure 14: Histograms represent the differences between Left (black bars) and Right (white bars) in COP_ML (A); COP_AP (B); COP_AREA (C); COP_SPEED (D). Asterisks show significant differences ($p<0.05$).

An interaction effect "Group by Side" was found for the COP_{ML} ($F_{2,231}$ = 15.03, p<0.001, ηp^2= 0.11), COP_{Area} ($F_{2,231}$ = 4.69, p=0.010, ηp^2= 0.03) and COP_{Speed} ($F_{2,231}$ = 11.40, p<0.001, ηp^2= 0.09). The Bonferroni pairwise comparison showed that the Laser group presented a significant difference between sides in medio-lateral direction (COP_{ML}) (p<0.001) (Fig. 15-A). The Retinopathy showed a significant difference between left and right side in the COP_{Area} (p=0.007) (Fig. 15-C) and COP_{Speed} (p<0.001)(Fig. 15-D).

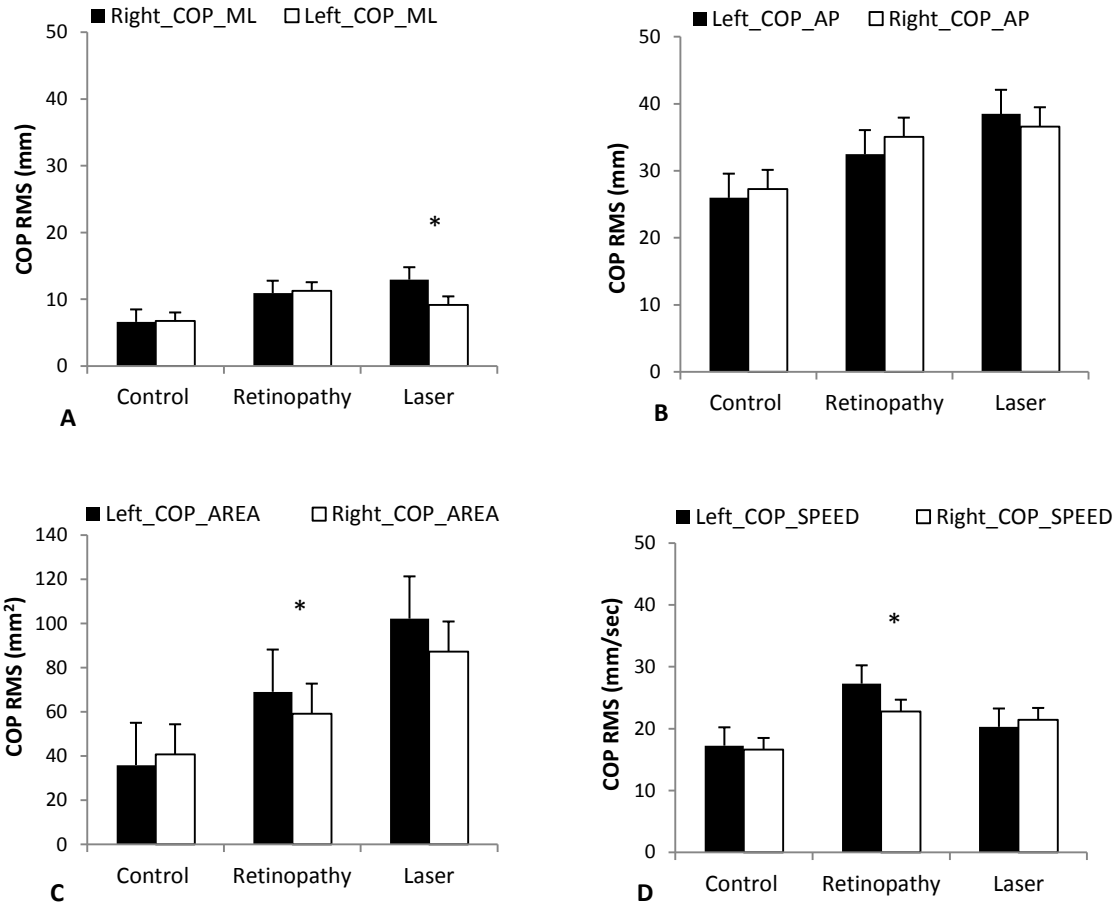


Figure 15 Histograms represent the differences in each group (Control, Retinopathy, Laser) between Left_COP (black bars) and Right_COP (white bars) in COP_ML (A); COP_AP (B); COP_AREA (C); COP_SPEED (D). Asterisks show significant differences (p<0.05).

As regards COP global data, figure 16 shows different COP_{net} traces in response to an optic flow stimulation in the foveal or in the peripheral visual field. The Control and the Retinopathy groups presented longer and disorganized COP_{net} traces in response to a foveal stimulation compared to a peripheral visual stimuli. In contrast, in the Laser group the COP_{net} traces were longer and more disorganized when the visual stimulus was presented in the peripheral portion of the retina.

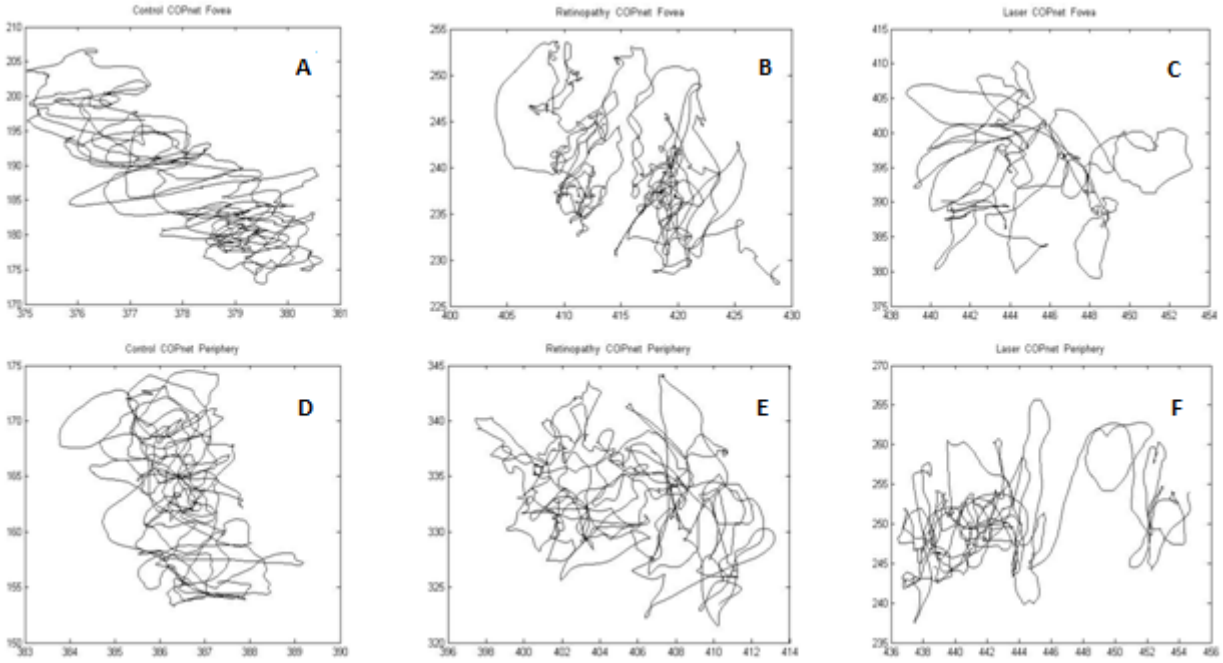


Figure 16: Comparisons between COPnet traces during Foveal and Peripheral optic flow stimulations in the Control group, in the Retinopathy group and in the Laser group. A) Control_Fovea. B) Retinopathy_Fovea. C) Laser_Fovea. D) Control_Periphery. E) Retinopathy_Periphery. F) Laser_Periphery. Trace drawings are scaled on the force platforms.

The results of the univariate ANOVA for Cop_{net} variables, revealed a significant "Group" main effect for COP_{net_ML} ($F_{2,231}$ = 25.21, p<0.001, ηp^2= 0.17), $COP_{net\text{-}\_AP}$ ($F_{2,231}$ = 23.66, p<0.001, ηp^2= 0.17), and COP_{net_Area} ($F_{2,231}$ =63.64, p<0.001, ηp^2= 0.35).

The Laser group showed significantly higher values of COP_{net_ML} compared to the Retinopathy group (p<0.001) and the Control groups (p<0.001) (Fig. 17-A). On the contrary,

COP_{net_AP} values were significantly lower in the Control group compared to the Retinopathy ($p<0.001$) and the Laser group ($p<0.001$) (Fig. 17-B). As regards $COP_{net\text{-}Area,}$ the laser group showed significantly higher values compared to the Retinopathy ($p<0.001$) and the Control groups ($p<0.001$), while at the same time the Retinopathy group presented higher values compared to the Control subjects ($p=0.002$) (Fig.17-C). We did not find any significant stimulus effect.

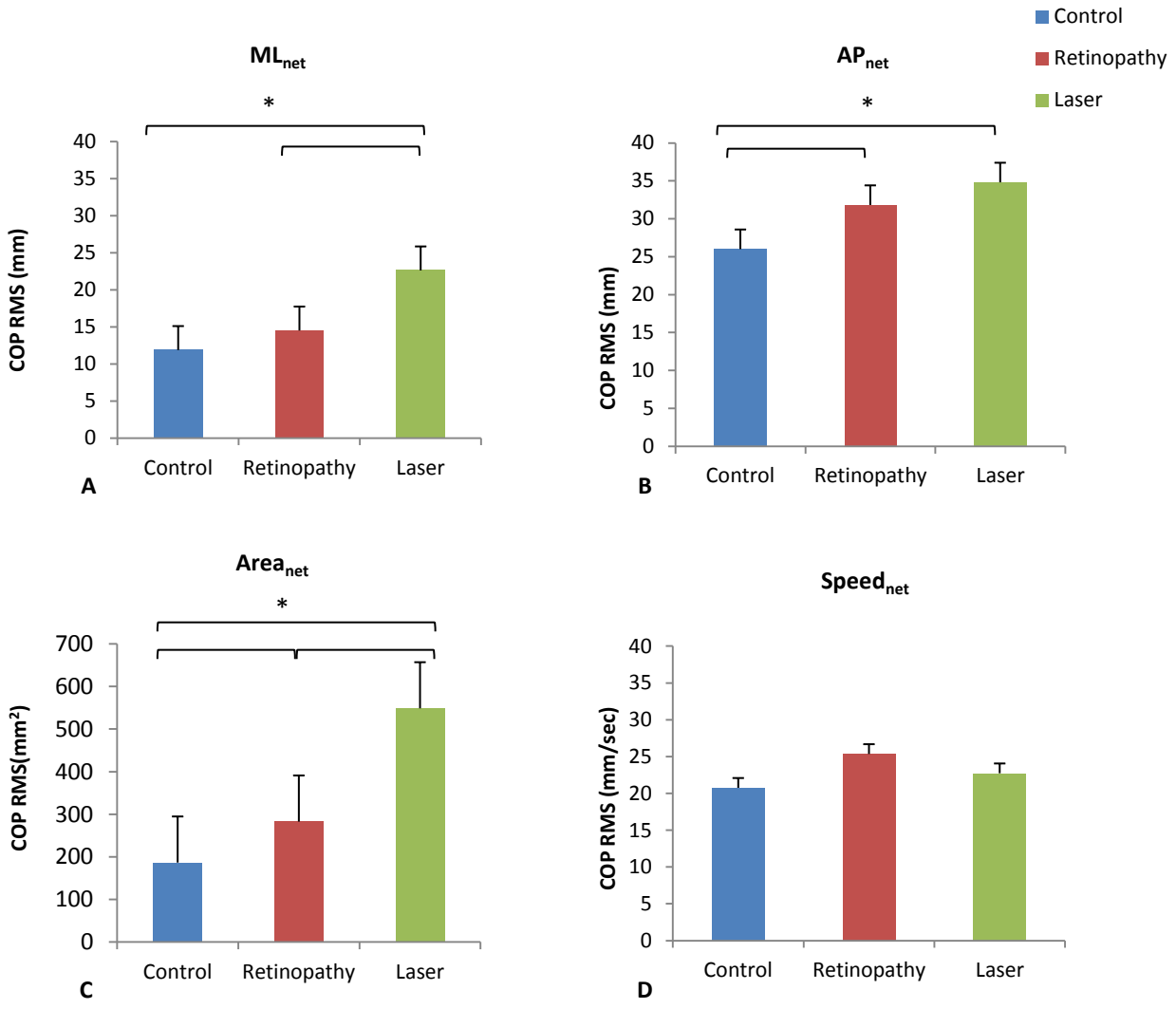


Figure 17: Histograms represent the differences between group Control (blu bars), Retinopathy (red bars) and Laser (green bars) in COP_{net} variables: ML_{net} (A); AP_{net} (B); $Area_{net}$ (C); $Speed_{net}$ (D). Asterisks show significant differences ($p<0.05$).

6.7.2 SURFACE ELECTROMIOGRAPHY

The repeated measures ANOVA (see Methods) applied to the normalized RMS values of each muscle in each stimulus revealed a significant main effect for "Group" ($F_{2,217}$= 9.43, p<0.001, ηp^2=0.80) and "Muscles" ($F_{1,217}$ =6.94, p=0.009, ηp^2= 0.31). Post-hoc tests showed significant differences between Control and Retinopathy (p<0.001) groups and Laser and Retinopathy (p=0.002) groups. We did not find significant difference in the muscle activation between the Control and the Laser group (Fig. 18-A). As regards the difference between muscles, the soleus muscle was the most activated, compared with the anterior tibialis. (Fig. 18-B).

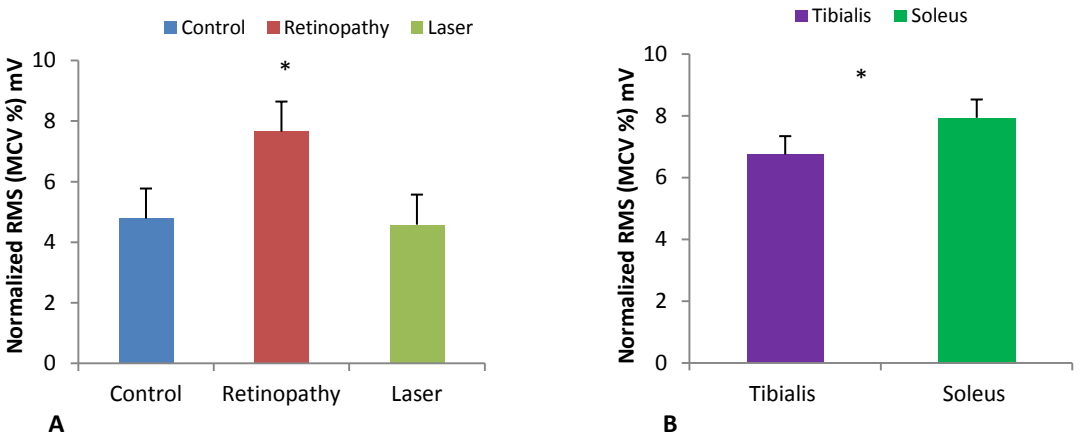


Figure 18: (A) The histogram represents the differences in muscle activation between groups Control (blu bars), Retinopathy (red bars) and Laser (green bars). (B) The histogram on the right was representative of the difference between muscles anterior tibialis (in purple) soleus (in green). Asterisks show significant differences (p<0.05).

We found also significant interaction effects: "Side by Group" ($F_{2,217}$= 10.52, p<0.001, ηp^2= 0.89), "Muscle by Side" ($F_{1,217}$= 11.60, p=0.001, ηp^2= 0.51), and "Muscle by Side by Group" ($F_{2,217}$= 3.66, p<0.027, ηp^2= 0.33). The Bonferroni pairwise comparison revealed that the Control group activated predominantly the right side (p<0.001) while the Retinopathy group activated the left side (p<0.001). No side effect was find in the Laser group (Fig. 19-A). As regards the interaction effect "Muscle by Side", we found this in the left tibialis (p=0.016). No significant differences were found between the left the right soleus (Fig. 19-B).

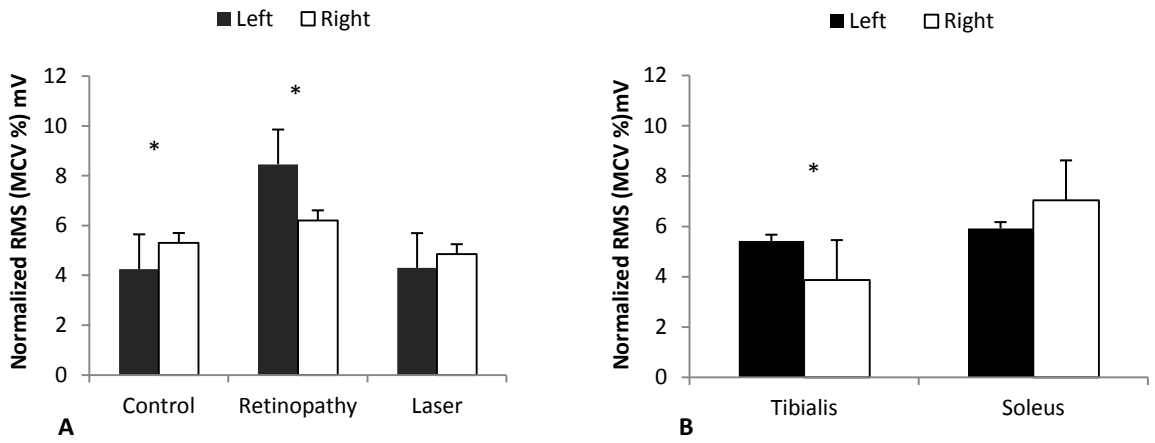


Figure 19: (A) The histogram on the left represents the difference between left side muscles (black) and right side muscles (white) in each group (Control, Retinopathy, Laser). (B) The histogram on the right represents the differences between left side (black bars) and right side (white bars) in the tibialis and soleus. Asterisks show significant differences ($p<0.05$).

Considering the interaction "Muscle by Side by Group" we found that the Control group activated predominantly the left tibialis ($p=0.014$) and the right soleus ($p<0.001$) while the Retinopathy group activated significantly more the left tibialis ($p=0.004$), but no significant difference was find between the right and the left soleus. The Laser group did not show any significant differences between side or muscle activation (Fig. 20). We did not find any significant stimulus effect.

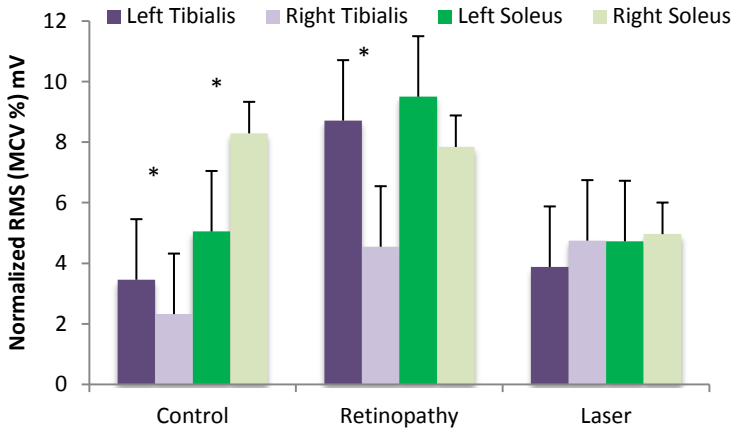


Figure 20: The histograms represent the differences between left tibialis (purple) and left tibialis (light purple) and between left soleus (green) and right soleus (light green) in each group (Control, Retinopathy, Laser). Asterisks show significant differences ($p<0.05$).

6.8 DISCUSSION

The aim of this research was to assess how optic flow stimuli contribute to the control of stance in people with different retinal functionality. We tested whether the dimension of the visual field stimulation can play a role in the postural stabilization process and verified whether it requires the predominant activation of cortical networks or the intervention of subcortical loops.

We performed the experiments in subjects with retinopathy and subjects with laser retinal treatment and we registered COP oscillation and muscles activation (anterior tibialis and soleus) in response to an optic flow stimulation. Researchers have used optic flow stimuli in order to produce a self-motion perception for evaluating the correlated postural readjustments [172]. Two main postural stabilization strategies (hip or ankle) can be recognized in response to different COP sway amplitude [107, 191, 192]. Until now, to our knowledge, no study has addressed the role of the perception process in determining specific postural responses in people with diabetic retinopathy, a complication of diabetes which affects retinal function [61]. The literature demonstrates that visual acuity and visual field seems to be correlated with the severity of diabetic retinopathy [66]. For this reason, we manipulated the spatial distribution of dot speed as well as changing the stimulus dimensions to stimulate specific heading directions and different portions of the retina.

Our results showed that people with diabetic retinopathy, and to a greater extent people with diabetic retinopathy who have received laser treatment, were more unstable than healthy control subjects. We have to remember that laser treatment leads to a loss of retinal receptors, mainly in the peripheral visual field [57, 67, 193]. The literature has widely demonstrated the functional importance of the peripheral retina in postural stabilization [142] and its preference for processing forward motion [194]. In the periphery, centrifugal movements are more readily detected that centripetal movements [144], subsequent to an adaptation of the visual system to the foveofugal patterns that are continuously experienced during locomotion or forward movement [194]. Our

optic flow stimuli had a characteristic pattern of expansion that simulated a forward motion in full visual, foveal and peripheral fields [24]. The great amplitude of the body sway observed in the retinopathy group, and especially in the laser group, could be an expression of the difficulty for this population in processing this kind of visual information. An impaired retinal function might negatively affect postural control in a way that is dependent on the severity of damage on the retina.

As already stated in previous research studies [195, 196], we found that COP_{net} oscillation in antero-posterior direction (COP_{net_AP}) presented a greater amplitude compare with the oscillation in the medio-lateral direction (COP_{net_ML}).

Furthermore, it seems that oscillation in the antero-posterior (AP) direction depends more on visual information than medio-lateral (ML) sway. Perrin et al. have demonstrated that the condition of having the eyes open versus eyes closed had very little effect on postural maintenance in ML, while postural stabilization in AP direction was significantly enhanced when the eyes are open [196]. Also other studies suggested that changing the characteristics of the visual field alters the postural responses in COP_{AP} but does not affect COP_{ML} [194, 197]. At the same time, this statement seems to be consistent with our observation of COP_{net_ML} and COP_{net_AP} sways in the retinopathy group and in the laser group when compared to the healthy control group.

The retinopathy and laser groups showed similar COP_{net_AP} sways compared to the control group. Conversely, we did not find any significant difference in the values of COP_{net_ML} between the retinopathy group and the healthy control group, while the laser group consistently showed the highest values. These results confirm the functional importance of the peripheral retina in postural stabilization. The lack of the peripheral retina (laser group) seems to induce a significant wider COP sway in the medio-lateral direction that was absent in subjects in a normal condition or at early stage of diabetic retinopathy. The differences in these two parameters guided us to understand the

functional significance of different retinal damage in changing the visual perception of optic flow and consequently the associated motor responses and COP dynamics.

COP_{net_Area} results are representative of the enclosed area covered by the COP as it oscillates within the base of support [186]. COP_{net_Area} takes into account the sways in both medio-lateral and antero-posterior directions and defines the overall postural instability experienced by the sample we are observing [198]. In common with the other COP_{net} variables, in the COP_{net_Area} the laser group showed the highest values followed by the retinopathy group and the control group. The literature demonstrates how unsteadiness tends to be related to the availability of the sensorimotor information [118, 126, 199, 200]. Complications associated with diabetes lead to a lack of one or more sensory information in entrance to the postural system [201], a condition which predisposes this population to a fall risk 15 times greater than compared to age-matched healthy adults [104]. In the same way, our data suggest that postural instability was proportionate to the retinal damage and altered or absent visual information could have negative effects on the postural system. As regards COP velocity (COP_{Speed}), the literature reports that this is proportional to the postural unsteadiness experienced [202]. It has been widely confirmed that people at high risk of falling present high values of COP_{Speed} [203]. Unexpectedly, despite the difference in the COP amplitude related to the severity of the retinal functional impairment, retinopathy and laser group showed a COP speed similar to the healthy control group. In our case, the low values of COP velocity (COP_{Speed}) as well as the lower values of muscle activity (tibialis and soleus) in the laser group were difficult to interpret if we observe the amplitude of their COP sway. We can hypothesise that they use a hip strategy for maintaining balance. Although we did not record the activity of the hip muscles, it could be a possible explanation if we considered that hip strategy is used to responding to greater COP perturbations [191]. We can propose two hypotheses: firstly, damage to the peripheral retina would alter the visual perception of self-motion and consequently there would be a discrepancy

between optic flow parameter and associated muscular responses. In addition to this, the absence of differences between the muscular activation of the tibialis and soleus is in agreement with a previous study, which affirms that older adults decrease their body sway by co-activating their muscles around the ankle joint, probably because of the danger of their postural instability [204]. The greater COP displacement perceived by the laser group might result in a compensatory leg muscle co-contraction in order to reduce COP_{Speed}. Once more, the postural responses, considered as the amount of linear or angular body displacement in response to visual stimulation [194, 205] or body velocity [206, 207], seem to be more related to the quality and quantity of the somatosensory information than to the specific characteristics of the visual information [96, 200, 208, 209].

The analysis of the contribution of each side (foot) in the maintenance of postural stabilization, a significant "side effect" and an interaction "side by group" effect showed differences between left and the right in postural stabilization. We observed asymmetries between the two limbs in the postural maintenance showing different dynamics in almost all COP parameters, characteristics already observed in younger cohorts [141, 172]. This asymmetry highlights the important fact that each foot has its own role in balance control [190]. At the same time, the different lateralization of postural controls suggests an asymmetry in postural balance due to different coordination between muscles of the right and left side [141, 172].

When we observed the different patterns of muscle activation and tried to re-create the specific strategies adopted by the groups, we found that the healthy control group responded to postural perturbation using a mixed strategy, activating predominantly the left tibialis and the right soleus, whereas the retinopathy group activated predominantly the muscle of the left leg. In contrast, the laser group did not show a preferred side of muscle activation. These postural strategies seem to correspond to different levels of retinal functionality evolving into a progressively lower level of adaptability and increased rigidity. The healthy control subjects

presented differences between muscle and side, while the retinopathy group had only a preferred side of muscle activation, and the laser group activated the agonist and antagonist muscles of both legs in the same way. Furthermore, the postural strategies did not change under different optic flow stimulation but we found specific postural stabilization strategies for a determinate retinal functionality condition. The absence of a different muscular response suggests that the availability of an optic flow stimulation seems not to play a role in triggering the preparatory muscle action; once a structured plan has been acquired, the relevant muscles respond relative to the task of maintaining posture. Also, previous studies did not find any stimulus effect in changing COP parameters and/or postural muscles activation [141, 172], so the main role of cortical mechanisms in the maintenance of stance has become increasingly evident. It has been shown that the pattern of postural responses evolves with age towards an improvement in stability performance and shorter sway latencies [210]. Children's and adults' postural control systems are different because they correspond to different maturity and different postural coupling with optical flows [211]. This demonstrates how postural control seems to be correspondent with learned behaviour based on experience. At the same time, the different postural strategies, as a consequence of different retinal functionality, seem to be pre-determined and dependent on cortical signal processing. The feedforward mechanisms include signals that are able to anticipate disturbances to the postural balance that will arise as a consequence of movement [167].

The literature demonstrates that the human body adopts open-loop control mechanisms over the short-term time interval and the closed-loop control mechanisms over the long-term to maintain quiet stance [47, 169]. An open-loop control system (feedforward) is characterized by the absence of sensory feedback; on the contrary, a closed-loop control system operates with sensory feedback, such as vestibular, visual and somatosensory systems [212]. Other studies reported that feedback control alone is insufficient to explain human postural control [168]. Some others studies have

suggested an important role for predictive mechanisms [213] or have concluded that nonlinear mechanisms combining open- and closed-loop control are used for stance control [169]. In our case, the absence of online readjustments in response to different optic flow stimuli presentation means that the intervention of sub-cortical mechanisms corresponding with feedback systems did not play a predominant role in the control of posture in a static condition.

Alongside the previous finding that showed how postural strategies differ between males and females because of the anatomical and biomechanical characteristics [172], we hypothesise that the differences in retinal function could have a role in affecting the postural system. Altered visual information due to the presence of a laser scars within 20° of the visual fields has been correlated with steeper brake response slopes, increased brake pressure and longer response times for braking [72]. These evidences shed light on the existence of a direct link between visual perception and motor action. However, the organization of these control mechanisms is still unknown, as is whether these mechanisms play a dominant or a minor role in postural control.

6.9 CONCLUSIONS

People with diabetic retinopathy and to a greater extent people with laser-treated diabetic retinopathy, showed a higher postural instability compared to healthy control subjects. In particular, people with a lack of peripheral retinal receptors demonstrated greater instability and a lower level of muscle activation. Different retinal functionality seems to influence postural attitude and muscle pattern recruitment. The difference in site (peripheral or foveal) and integrity of the neuroretinal in which optic flow information are processed seem to have a predominant role in affecting the postural control system.

Results of the present study indicate that different optic flow stimuli do not have an effect on muscle activity, however, people with different retinal functionality seem to perform adaptive stabilization motor programmes based on the characteristics of visual perception.

Results seem to suggest that the same postural assessment for different optic flow stimulations is mainly dependent on cortical processing mechanisms. This result sheds light on the motor control system that influences postural response.

7 STUDY II

The second part of my research project, entitled “Driving and Diabetes”, was supervised by Professor Neil Revees, Professor of Musculoskeletal Biomechanics, and Professor Dilwyn Marple-Horvat, Professor of Motor Neuroscience at Manchester Metropolitan University. During the last year of my PhD, I spent 6 months at Manchester Metropolitan University where I undertook all the steps of this research study (recruitment, data collection and data analysis). I recruited people with diabetes without neuropathy by email and letters using the “Research for the Future: Help BEAT Diabetes” database. I recruited people with diabetic neuropathy in person at the Manchester Diabetes Clinic and the Foot Clinic, NHS Foundation Trust. Experiments were all conducted in the “Motor control” laboratory“ and the “Musculoskeletal laboratory” of the School of Health Care Science of the Manchester Metropolitan University.

7.1 INTRODUCTION

Diabetic peripheral neuropathy (DPN) compromises the function of both sensory and motor nerves [87] with implications for many aspects of movement involved in daily life activities [126, 127]. The sensory system is composed of several different muscles, joints and cutaneous mechanoreceptors; the information from these receptors is integrated in the central nervous system to produce a sensation of joint position and movement. The most affected target of diabetic peripheral neuropathy is the foot, which is rich in proprioceptors and tactile receptors. An altered function of muscle spindles negatively affects ankle movement perception at the joint ankle level [95, 102, 214]. Furthermore, the loss of II type afferents, sensitive fibres that transmit information regarding muscular tone, could be one of the major contributing factors to postural instability [92, 112]. The impairment of the graviceptors, receptors which, together with otoliths, provide information about the head-trunk alignment with respect to the gravitational vector [215], modifies the vestibular-podal interaction involved in the control of automatic responses and the reflexes

involved in the maintenance of equilibrium [216]. In response to small perturbations people with diabetic peripheral neuropathy shift from a physiological ankle postural strategy, usually observed in healthy control subjects, to hip-based postural control. These changes seems to be due to a progressive loss of function of the muscles at the ankle level [93, 217].

The reduced nerve conduction velocity of peroneal and sural nerves significantly correlates with muscle response latencies and reduction of muscle strength, which together represent concomitant factors contributing to postural instability in DPN patients. Furthermore, DPN people exhibit muscle strength values at the ankle dorsal and plantar flexors 40% lower than diabetic patients without neuropathy. The annual strength loss can vary between 3% - 6% depending on the degree of neuropathy [218].

A decline in the ability to control these muscles, together with the lack of adequate proprioceptive feedback and a reduced range of motion (ROM) at the ankle lead to an altered distribution of the load at the plantar foot level in both static and dynamic conditions [92, 95, 112, 219]. DPN patients walk more slowly and with a wider stance showing a significantly slower strength generation at both the ankle and knee joints and altered muscle activation timings during stair ascent and stair descent [124, 126, 220].

Recent studies have demonstrated that lower-extremity sensorimotor neuropathy patients had slower mean brake response times during driving and an increased frequency of abnormally delayed brake reactions, compared to diabetics without neuropathy and to healthy control subjects [122, 123]. Although walking is a fundamental task at the heart of everyone’s daily routine, driving a car is another good example of a routine daily task for many people, which also requires adequate sensory-motor function for optimal performance [221].

7.1.1 THE DRIVING TASK

Driving is an everyday example of visually guided behaviour in which the eyes move in coordination with another action (steering) [222]. On a winding open road, a driver consistently looks to the inside of each bend half a second or more before turning the steering wheel. The horizontal component of gaze is attracted to and lies upon that "tangent point" [223]. This oculomotor coordination seems to be innate, thus suggesting that it represents optimal coordination, and it reflects the ways in which the central nervous system has solved the problem of steering combining all information arriving from the peripheral nervous system. When researchers have tried to disrupt this coordination, by instructing drivers not to move their eyes, the drivers performance was impaired and their completion time during racing increased [121].

The pattern and duration of eye movements are highly specialized for each situation and affect performance of actions [222, 223]; the degree of coordination between eye movements and other actions, and their relative timing largely determine performance [119]. The eye signal provided by the proprioceptors of the ocular muscles or the "efference copy" of the oculomotor controller (i.e. the collection of the centre that together produce and control eye movements) is an input that can guide eye-steering movements [121]. Signals from the manual control system appear to be sent to the ocular control system, to provide predictive information about the required hand movements [224].

It is probable that by studying the neural circuits implicated in the integration of the oculomotor and motor response at the cerebellum level [129], we could better understand its fundamental role in driving performance [224, 225]. The cerebellum is known to have important functions in motor control, coordination, motor learning and timing. It can be defined as the "sensory predictor" responsible for generating predictions about the sensory consequences of motor acts. Predictions about the sensory outcome of movements can be used to generate specific motor

output [224]. The cerebellum provides the central nervous system (SNC) with a neural “forward model”, a necessary component of the process of oculomotor coordination. This forward model avoids the feedback delays in the real-sensory motor apparatus, and functions as a near-optimal feedforward controller [1].

Six extraocular muscles (four rectus muscles, two oblique) innervated by three cranial nerves (abducens nerve VI, trochlear IV and oculomotor nerve III) are responsible for the control of gaze. Saccadic eye movements consist of a hierarchy of behaviours, from passive rotation in darkness, to reflexive saccades made in response to the sudden appearance of a novel visual stimulus, through to high level volitional behaviour such as saccades directed towards the remembered location of a visual target. Saccades are defined as rapid eye movements that shift the line of sight between successive points of fixation [226].

The ocular motorneurons encode the characteristics of the saccade in terms of their temporal discharge, i.e. the size of the saccade is proportional of the total number of discharge spikes. The high velocities reached during saccades ensure that their duration is kept very short, ranging from approximately 30 ms for a 5°movements to 100 ms for 40° saccade. In this way, the period of visual disruption resulting from saccadic eye movements is minimized. During saccades, the observer is effectively blind owing to limitations of photoreceptor response time course and to active suppression of the visual pathways during these eye movements.

Two types of neurons are critical components of the brainstem network that generates premotor commands for saccades: burst neurons and omnipause neurons. The burst neurons for the horizontal saccades lie within the paramedian pontine reticular formation. These cells fire at a high frequency just before and during ipsilateral saccades. A second class of pontine cells, the so-called omnipause cells, fire continuously except during the saccade execution; firing ceases shortly before and during saccades. This cells are located in the dorsal raphe nucleus [226]. As eye movements are

a component of cognitive behaviour and the decision when and where to make a saccade is usually made in the cerebral cortex, the superior colliculus, a multi-layered structure in the midbrain, integrates visual and motor information into oculomotor signals to the brain stem. The superior colliculus is controlled by two regions of the cerebral cortex that have different but overlapping functions in the saccade generation: the lateral intraparietal area of the posterior parietal cortex (part of the Broadmann 7) modulates visual attention and the frontal eye field (part of Broadmann's area 8) provides motor commands.

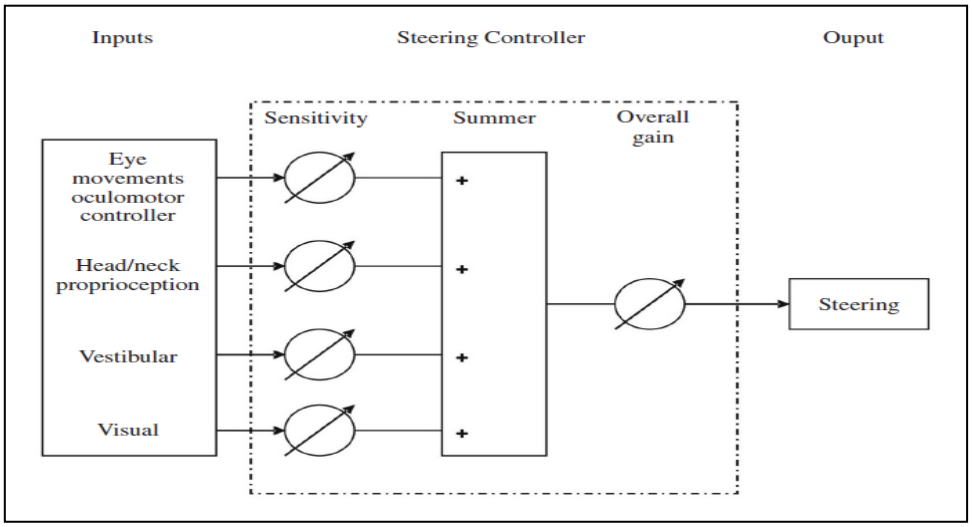


Figure 21: This scheme provides evidence of the multisensory command that guide the process of steering during driving. Varying independently the sensitivity of each input, we can act on steering-wheel coordination (Wilson, 2008).

When considering the control of the pedal we found a variety of studies, which investigated the human perception-brake reaction times (RT) in different situations and pathological conditions [227-229]. However, by analysing a large number of data sets, it is possible to estimate a recommended safety threshold of 0.70 seconds. This time interval increases in the presence of conditions in which there is impaired musculoskeletal function and/or impaired physiological biomechanical and kinematic function of the lower limb and/or the foot [122, 228, 229]. In normal conditions, an emergency braking configuration could be defined as: 1) joint flexion angles of 96◦,

56◦ and 13◦ for the right hip, knee and ankle respectively; 2) a maximum brake pedal load of 780 N; 3) a muscular activation of 55% for the anterior thigh, 26% for the posterior thigh, 18% for the anterior leg and 43% for the posterior leg [230].

7.2 AIMS OF STUDY II

The evaluation of skills during functional activity provides further information about the capacity of patients in order to understand whether neuropathy interferes with daily life activities which require sensorimotor integration [231]. We wanted to evaluate people with and without diabetic neuropathy compared to healthy control subjects during a driving test using a simulator to verify to what extent diabetes and diabetic peripheral neuropathy affect the ability to drive when considering both eye-steering wheel coordination and pedal control.

Diabetic people, and to a greater extent people with DPN, develop a slower rate of joint torque production (RTD) at the ankle compared to matched controls. What is more, diabetic peripheral neuropathy-impaired proprioception function seems to be the main factor in contributing to unsteadiness in this cohort [109]. Besides their poor proprioception function and/or incapacity to express strength rapidly; people with DPN also have an altered visual gaze strategy, which might be the cause of their relatively poor stepping accuracy performance [125].

Based on these findings, we hypothesized that this population might have at least the potential for impaired driving function. Driving a car requires a good eye-steering coordination [119] as well as a precise control on the pedal in term of strength and joint movement perception [232]. Furthermore, recent studies supported our hypothesis in part and demonstrated that lower extremity sensorimotor neuropathy patients showed slower mean brake response times and increased frequency of abnormally delayed brake reactions compared with diabetics without neuropathy and compared with healthy control subjects [122, 123].

Given the importance of eye movements for optimal and safe driving performance, we aimed to determine whether diabetes is associated with alterations of visual gaze behaviour that might adversely affect driving performance. We asked to all participants to drive a driving simulator while a remote infra-red camera (eye-tracker) was tracking their eye movements. We quantified eye movements in relation to driving performance and examined possible differences between the three experimental groups. We used a correlation coefficient (r^2), which defined the degree of oculo-manual coordination and a time lead (tL) value, which represented the lead time of eye movements over steering wheel movements across the drive period.

In order to identify the different contributions and/or the impairment of the proprioceptive and motor function during a driving task, some motor control measures on a dynamometer (rate of torque development ”RTD”, peak torque ”PT”) and within a driving simulator test were compared. We hypothesized that a decline in the ability to control ankle and plantar flexor muscles, together with the lack of adequate proprioceptive feedback could negatively influence driving performance. During fast ankle excursion, therefore, short contraction times may not allow maximal muscle force to be reached so, speed of strength generation (rate of torque development, RTD) could be a determinant for driving performance. The maximal rise in muscle force (rate of torque development, RTD) has important functional consequences as it determines the force that can be generated in the early phase of muscle contraction (0-200ms). The overall force of contraction depends on both the number and size of active motor units and their individual firing rates [233]. It has been shown that the discharge rate of motoneurons influences not only the magnitude of contractile tension, but also RTD [233]. Electrophysiological studies in diabetic patients showed that muscle strength correlated with fibre density and amplitude of the macromotor unit potential, suggesting incomplete reinnervation after axonal loss [234]. Furthermore, longitudinal studies suggest an average loss of compound muscle action potential amplitude at a rate of 3%/year in patients with type 2 diabetes

over a 10-year period [235]. We sought to determine whether ankle function specific to pedal control in driving is altered in people with and without diabetic neuropathy. Even though the effects of DPN on gaze, muscle strength, proprioception have been scientifically demonstrated, no study, to our knowledge, have been designed to investigate possible relationships among these factors. The innovative part of this research project is in the comparison of multiple data (usually taken separately), to find a clear connection between the different parts involved in sensorimotor integration in the process of driving, to work towards an objective assessment of fitness to drive with diabetes, based upon neurophysiological variables.

7.3 RESEARCH DESIGN AND METHODS

7.3.1 PARTICIPANTS

Fifty-four participants, all active drivers were recruited into three groups: 15 participants with DPN [DPN group mean ± SD, 66 ±6.0 BMI 32 ± 4.2], 25 participants with diabetes but no peripheral neuropathy [DM group 62 ± 8.7, BMI 31 ± 5.2] and 14 healthy aged-matched control subjects without diabetes [Control group aged 58 ± 10, BMI 27 ±4.4]. All participants gave their written consent to participate in this study, which was given ethical approval from the relevant bodies. The principal inclusion criteria in participants were: diagnosis of diabetes (diabetes groups) or absence of diabetes in the control group (confirmed via random blood glucose test <7,8 mmol/l); holding a current full UK driving licence; driving a car at least once per week; and aged over 20 years. The principal exclusion criteria were: 1) active foot ulcers on either foot, 2) lower limb amputation involving more than two toes on the right foot, 3) dementia, 4) visual acuity worse than 20/50, 5) proliferative retinopathy.

7.3.2 DIABETIC PERIPHERAL NEUROPATHY ASSESSMENT

The presence and the severity of the neuropathy was measured using the modified Neuropathy Disability Score (mNDS), a composite test of multiple sensory modalities and the detection of the vibration perception threshold (VPT) using a neurothesiometer (Bailey Instruments Ltd. Manchester, U.K.). The mNDS ranges from 0 to 10, with 0 being detection of every sensation applied to the feet and 10 meaning a complete lack of sensory perception in the feet. The VPT ranges from 0 to 50 Volts (50 indicating a complete lack of sensory perception in the feet) [51] (Fig.22). Based on these tests, diabetic participants were divided into two groups according to the following criteria: DPN group mNDS score of $\geq$6 and a VPT of $\geq$25 Volts; DM group, mNDS score of $\leq$3 and a vibration perception threshold of $\leq$15 Volts. These tests were also performed in the control group to confirm the absence of peripheral neuropathy from any aetiology .

Figure 22: On the left, the tool kit used to assess the Neuropathy Disability Score (mNDS): 1) a pen with each side different in temperature (cold and warm) to test temperature perception; 2) a blunt needle (pin prick) to test pain perception; 3) a tuning fork to test vibration detection (128Hz); 4) a reflex hammer to test the presence of the Achilles tendon reflex. On the right, the neurothesiometer (Bailey Instruments Ltd. Manchester, U.K.) used to detect the Vibration perception threshold (VPT).

7.3.3 PROCEDURE

During a 2.5 hour experimental session, each participant underwent a series of tests, which were always presented in the same order. First, a random blood glucose test was performed to confirm the absence of diabetes in controls and to avoid hypo- or hyperglycaemia conditions in

diabetes patients. Only diabetes participants with blood glucose levels within the range 4.5 to 20 mmol/l undertook the driving simulator test. Information was taken about each participant's medical history and, maximum isometric muscle testing and a proprioception test of the plantar flexor muscles of the right leg were performed on a dynamometer (Cybex Norm, USA).

Before the driving simulator session we assessed visual acuity using a Snellen Chart (23 X 35.5 cm) with traditional optotypes. Visual acuity range 20/200 to 20/20 was tested at 3 metres distance [236]. Corrected visual acuity had to be ≥ 20/50 since this is defined by the World Health Organization as "moderate visual impairment".

7.3.4 APPARATUS

All measurements of motor function (maximum isometric muscle contraction, proprioception test) were completed using a dynamometer (Cybex Norm,Usa) (Fig.23). The dynamometer was integrated with a data acquisition system Labchart 8® (AD Instruments Sidney, Australia). Participants were positioned prone on the dynamometer couch and their right foot secured to the footplate of the dynamometer, and a 0° neutral position (NP) was considered to be when the foot was at 90° with the tibia. Non-elastic straps was used to prevent changes in joint angle that would influence the length of the tested muscle and subsequently joint torque. The Prone position was chosen to isolate the plantar flexor muscles and reduce the recruitment of other muscles [237]. The centre of rotation of the dynamometer was visually adjusted to the right malleolus of the ankle. The dynamometer was set to move automatically the footplate in the desired ankle joint position.

Figure 23: The isokinetic dynamometer (Cybex Norm, USA) used to assess motor function variables.

RATE OF TORQUE DEVELOPMENT AND PEAK TORQUE

A joint torque is the turning force of the joint that both causes and controls movement. Rate of torque generation (RTD) at the ankle was measured as the rate at which joint torque was developed. Therefore the speed at which this force is developed is indicative of the speed at which strength is generated at the joint [126]. The maximal torque value of the plantar flexor muscles was defined by the value of the peak torque value (PT) reach during a maximal isometric contraction [238]. After several standardized submaximal contractions as a warm-up, participants completed a maximum effort isometric strength test of the plantar flexor (calf) muscles of the right leg at 0° neutral position (NP) and 10° of plantar flexion (PF). Participants were instructed to push against the dynamometer footplate using their plantar flexors (the action was demonstrated to participants) as hard and fast as possible, as they would on an emergency brake, and to maintain the contraction for ~3-5 seconds. The contractions were repeated twice with sufficient rest in between [239].

PROPRIOCEPTION FUNCTION

Proprioception is the knowledge of position (sense) of body parts in relation to one another. Proprioception function is mediated by muscle spindles, small encapsulated sensory receptors located in the fleshy part of the muscles. Their main function is to signal changes on the length of muscles within which they reside. Thus, these changes are related to modification in the angle of the joints, in fact the central nervous system use muscle spindles to sense the relative position of the body segments [1].

During the proprioception task, the ability to reproduce a specific joint position was objectively quantified using the dynamometer [102]. After the explanation of the task, the proprioception test included some practice trials at different joint ankle position to ensure comprehension of the task. The arm of the dynamometer moved passively at the target angle of 10 PF; ankle angles between 2◦ and 15◦ of plantar flexion in respectively normal and braking conditions were previously reported [240]. The participant's foot remained at this position for 5 seconds, then the dynamometer foot plate was moved into dorsiflexion and plantar flexion to disturb position sense and the participant was asked to move the foot to the target angle and remain in position for ~3 seconds. The task was repeated 3 times, with a 1-minute rest in between so as not to obtain false values, for example in response to an achievement of the task position as opposed to for a real improvement. Participants were unable to see their feet during the experiment.

DRIVING SIMULATOR TASK

We asked to all participants to drive a driving simulator while a remote infra-red camera (eye-tracker) was tracking their eye movements. The driving simulator consisted of a 42-inch plasma screen, a force feedback steering wheel, accelerator, and brake pedal system and rally car seat (Fig.24). The driving task was taken from the Colin McRae Rally 2 simulation (Codemaster, Leamington Spa, Warwickshire, UK), a driving environment simplified by the absence of other

vehicles and pedestrians. Participants were invited to find a comfortable position with adjustment of the simulator construct as needed for individual preference. Specific instructions were given to participants to “drive safely, as they would in a real car”. Verbal instruction and a demonstration describing how to use the simulator were given. The task consisted of driving the same route repeatedly to observe whether there was any improvement over the drives. Each driving sessions took about 30-40 minutes in total; variations depended on the participants own velocity during the 3 drives.

Figure 24: The driving simulator incorporated a 42-inch plasma screen, force feedback steering wheel, pedals and a car seat. The set-up also included an eye-tracking device, which monitored the driver’s eye movement, and a potentiometer attached to the steering wheel to monitor its rotation. Gaze, wheel and pedal raw data were visualized directly in real-time on monitor screens.

Sensors within the steering wheel and pedal were also present. Analogue signals of pedal acceleration and breaking, horizontal eye movement (calibrated to 1° accuracy), and steering wheel rotation were digitalized at 200 Hz using CED 1401A7D converter (Cambridge Electronic Design, Cambridge, UK). Eyes movement data were recorded using an eye tracking system ASL 504 (Applied Science Laboratories, Bedford, MA, USA) mounted at dash panel height. The “ASL

system" was designed to move and compensate for the normal small head movements that follow the course of the road, in order to maintain an accurate lock on the drivers' eyes. On occasions when the eye was briefly lost (mainly due to blinks) drop-out occurred in the horizontal eye movement until the system acquired the eye again. This was removed by manual interpolation and subsequently analysed using a "Spike® 2" script in order to produce a cross-correlogram of horizontal eye versus steering wheel movements. Before starting the data acquisition, a nine point calibration was performed in order to have information about the position of the eye in a coordinate system (x,y).

7.4 DATA ANALYSIS

7.4.1 DRIVING SIMULATOR TASK: EYE-STEERING COORDINATION

We obtained two values that quantified a driver's eye-steering coordination over the drive time. The correlation coefficient (r) defines the degree of coordination, and the time lead (tL) defines the interval by which eye movements lead steering wheel movements across the drive period**.** Cross-correlograms of horizontal eye vs steering wheel movements were generated using a Spike 2 script. Cross-correlation of the two signals over the time taken to complete a drive yielded a cross-correlogram, the peak of which identified the correlation coefficient (r) which is a measure of the covariation of the two signals (Fig.25).

Cross-correlation is a powerful technique for quantitative analysis of eye to steering wheel coordination. The correlation coefficient squared (known as the coefficient of determination r^2) is a measure of the amount of variability in one variable that is shared by the another one. In this case, wheel coordination might well share a % value of the variation with eye coordination.

Calculation of (r^2*100) yields the percentage of variance in steering wheel movement that is attributable to covariation with horizontal eye movement. This study used the same analytical

techniques as previously used in a realistic simulated driving task [119, 121]. Driving speeds were also take into account (mph).

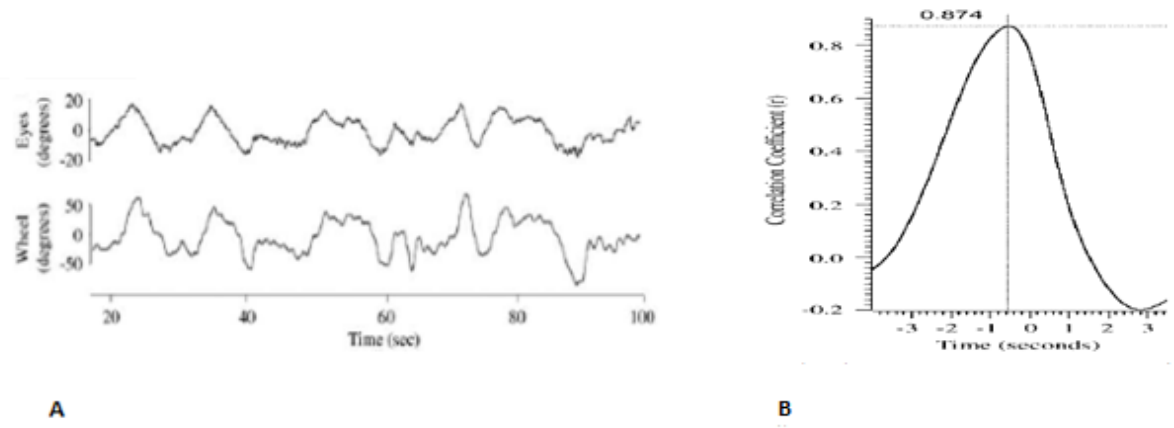


Figure 25: A) Raw data output reveals that the drivers' horizontal eye movements (above) were tightly linked to, and led, their turning of the steering wheel (below). B) An example cross-correlogram of horizontal eye and steering wheel movement of a drive. The y axis indicates the degree of covariation between the two signals (R)and the x-axis value indicates the time interval by which the eye and steering signal are offset (tL). The peak of the cross-correlogram identifies the degree and relative timing of any covariation.

7.4.2 RATE OF TORQUE DEVELOPMENT AND PEAK TORQUE

From the dynamometry test, the rate of torque development (RTD) was assessed as the gradient of the torque-time curve over a defined region of time (150ms) from the onset of contraction. Onset of muscle contraction was defined as the time point at which the moment curve exceeded baseline torque by 5 Nm. The RTD was derived as the average slope of the torque-time curve (Δtorque/Δtime) over a time period of 150ms relative to the onset of contraction. As regards RTD and peak torque we chose the higher values in the trials in two ankle positions (0°, neutral position "NP" and 10° of plantar flexion, "PF"). The trial in which highest peak value of torque was observed represented the peak torque (PT), and considered as the maximal strength value.

7.4.3 PROPRIOCEPTION FUNCTION

The number of degrees between the end position and the target position (10° PF) were recorded as error values (deg). At the end of the proprioception test, each participant had three error values. Finally, we calculated the percentage variation between the third and the first trial:

$$(\text{error value}_{\text{third trial}} - \text{error value}_{\text{first trial}})/\ \text{error value}_{\text{first trial}})*100.$$

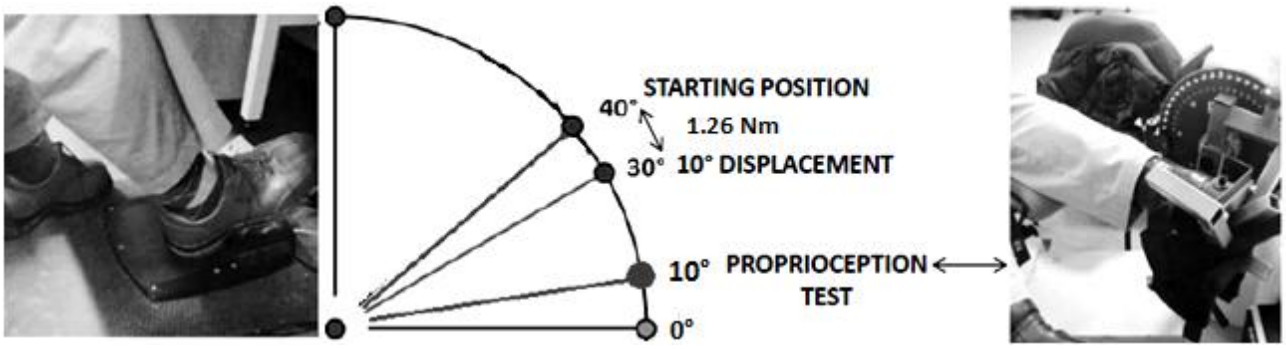


Figure 26: On the left the driving simulator pedal which has an inclination of 40° degrees relative to the floor. On the right, the proprioception test at the dynamometer. The proprioception function was tested at 10° (plantarflexion) in a prone position.

7.4.4 DRIVING SIMULATOR TASK: PEDAL CONTROL

The pedal signal was recorded over a range that went from 0° degrees, when no load was applied on the pedal, to a maximum of 20° when the pedal was completely pushed down. 1.26 Nm force was necessary to push it down about 10°. Acceleration and deceleration were quantified in term of pedal displacement. We considered the position of pedal (degrees) as functions of the pressure applied to it. High values of pedal displacement (degrees) corresponded to an increase in the pressure (acceleration), while lower values corresponded to deceleration. Firstly, we considered each complete drive as a whole in order to observe the trend of pedal usage during the drives and make some comparisons with the proprioception task. Then, we evaluated a specific time portion of the driving in order to identify differences between groups in pedal usage before and after a major

bend. We wanted to assess differences in the 3000 ms leading up to the bend (pre-bend) and for the 3000 ms after the bend. Lastly, we examined each drive individually in order to observe the trend of pedal usage during the drives and make some comparison with the proprioception task.

7.5 STATISTICS

The eye-steering coordination coefficient values (r^2%), the time lead value (sec.) and driving velocity were analysed using a repeated measures ANOVA in which drives (Drive 1 and Drive 2) were the within-subject factors and groups (Control, DM and DPN) the between-subject factors.

As regards motor function, variables RTD and PT were analysed using a one-way ANOVA in order to assess differences between groups for each joint ankle position (0° NP and 10° PF). Proprioception function was analysed using a repeated measures ANOVA in which trials (Trial 1, Trial 2, Trial 3) were the within-subject factors and groups (Control, DM and DPN) the between-subject factors.

Mean pedal values were analysed using a repeated measures ANOVA in which drives (Drive 1, Drive 2, Drive 3) were the within-subject factors and groups (Control, DM and DPN) the between-subject factors. Another repeated measures ANOVA was also performed to assess any differences pre/post bend on the pedal signal. Pedal values pre- and post-bend were set as within-subject factors, and groups as between-subject factors.

A Pearson cross-correlation was used in order to investigate the possible relationship between neuropathic test scores, motor function variables and pedal signal of the whole drive.

Bonferroni post-hoc tests were utilized to assess differences between groups. All statistical tests were analysed on SPSS statistical package (version 22, Chicago, IL, USA) with significance set at $p<0.05$.

7.6 RESULTS

DPN group presented significantly higher value for both the modified Neuropathy Disability Score, mNDS ($F_{2,52}$ =81.99, p<0.001, ηp^2 = 0.77) and the Vibration perception threshold, VPT ($F_{2,52}$=106.94, p<0.001, ηp^2 = 0.80) compared to DM and Control groups. There were no significant differences between DM and Control groups for both mNDS (p=0.082) and VPT (p=0.073) scores, confirming that people in the Diabetes group had no neuropathy (Table 1).

Group	Control	DM	DPN
Number	15	25	14
Age (years)	58 ± 10	62 ± 8.7	66 ± 6.0
BMI (kg.m^{-2})	27 ± 4.4	31 ± 5.2	32 ± 4.2
Duration of Diabetes (years)	_	16 ± 9	11± 9
VPT (V)	6 ± 3.19	11 ± 5.6	42 ± 10.3
mNDS (score/10)	0	2 ± 1.2	7 ± 2

Table 1: Characteristics of the three samples: Control, healthy subjects; DM, subjects with diabetes mellitus and no neuropathy; and DPN, Subjects with diabetic peripheral neuropathy.

7.6.1 DRIVING SIMULATOR TASK: EYE-STEERING COORDINATION

53% of participants with DPN, 64% of participants with DM and 85% of healthy control subjects managed to complete the drives and thereby generate data about eye-steering coordination. People who suffered from driving sickness during the task and was unable to complete the driving session were excluded from the data analysis. Three subjects were excluded because of the dimensions of the pupils were too small to be captured by the oculometer.

The repeated measures ANOVA (see methods) revealed a significant "Group" main effect in the eye-steering coordination values (r^2 %,) ($F_{2,33}$ =4.91, p=0.013, ηp^2 = 0.23). The Bonferroni post-

hoc demonstrated that the Control group differed significantly from both DPN (p=0.038) and DM groups (p=0.028) in eye-steering correlation values.

We did not assess any significant increase in (r^2%) between the first (mean±SE: DPN 54.73 ± 4.7; DM 50.99 ± 3.32 Control: 66.76±3.84) and the second drive (DPN 53.52 ± 4.19; DM 60.62 ± 2.96; Control 68.58 ± 3.42) p>0.05. (Fig. 27-A).

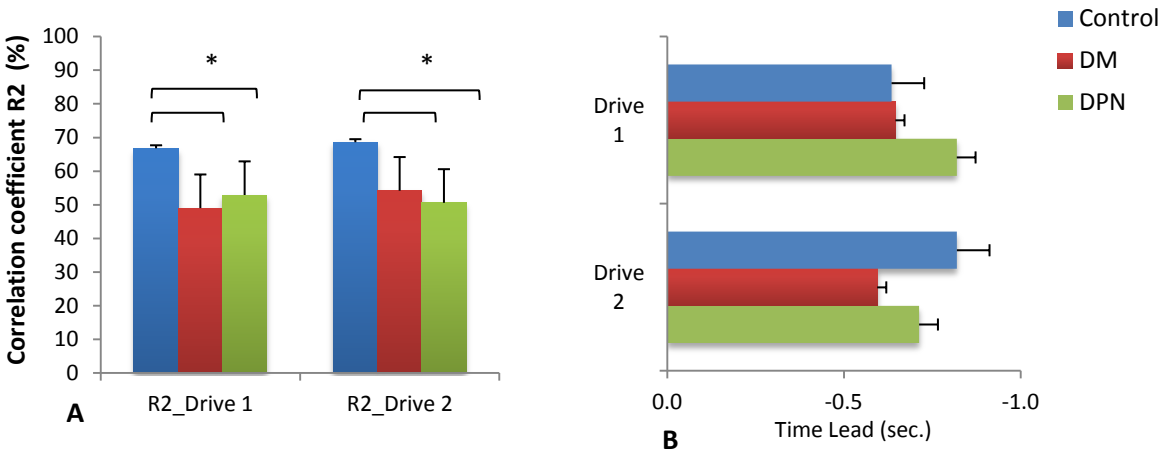


Figure 27: The histogram on the left (A) shows the different degrees of eye-steering coordination (R2%). The histogram on the right (B) represents eye lead time (sec) over steering wheel movements. Data refer to the same two drives (Drive 1 and Drive 2). The colours represent the Control group (blue bars), the DM group (red bars) and the DPN group (green bars). Asterisks show significant differences (p<0.05).

The repeated measures ANOVA (see methods) did not demonstrate differences in time leads (tL) between groups (DPN -0.76 ± 0.15; DM -0.62 ± 0.19; Control -0.72 ± 0.12, p>0.05) or between drives (mean;± DPN; p>0.05) (mean;±: DPN -0.71 ± 0.57; DM -0.59 ± 0.43; Control -0.82 ± 0.18; p>0.05) (Fig. 27-B).

As regards driving velocity (mph), we observed a main effect for "Drives" ($F_{1,33}$ =20.36, p<0.001, ηp^2=0.382). Velocity increased significantly looking at the first drive (DPN 31.44 ± 11.66; DM 38.23 ± 8.65; Control 38.64 ±8.52) respect to the second drive (mean;±: 35.02 ± 11.02; DM 40.18 ± 8.88; Control 39.61 ± 7.84).

7.6.2 RATE OF TORQUE DEVELOPMENT AND PEAK TORQUE

The analysis of the rate of torque development revealed a main effect for "Group" at 0° (neutral position, 0°NP) ($F_{2,51}$ =7.04, p=0.002, ηp^2=0.21) and at 10° plantarflexion (10° PF) ($F_{2,51}$ = 9.22, p<0.001, ηp^2=0.26). DPN and DM showed significantly lower values of RTD compared to Control at 0° (neutral position,0° NP) and at 10° plantarflexion (10° PF). No significant difference was found between diabetic patients with and without neuropathy (p>0.05) (Fig. 28).

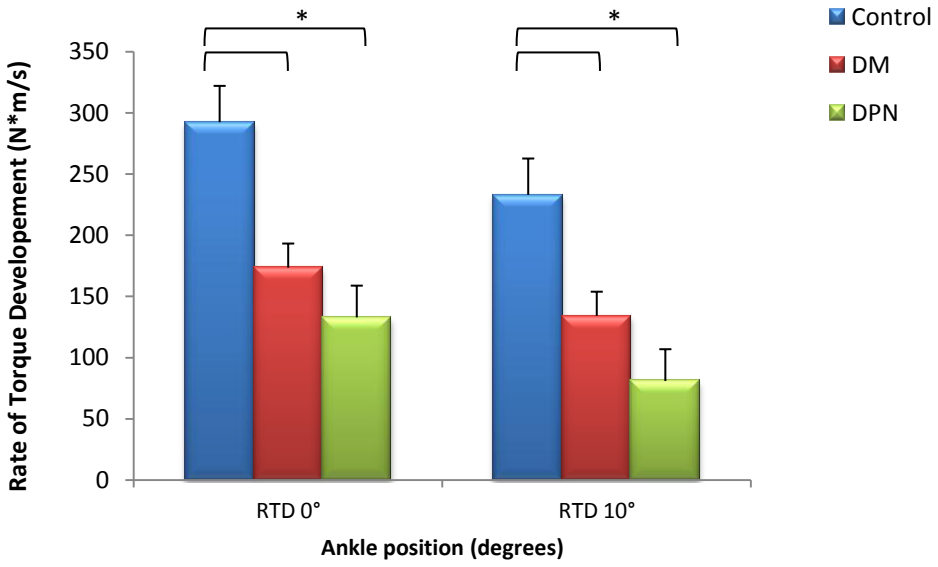


Figure 28: The histograms above display the Rate of torque development (RTD) values registered during the first 150 ms of the maximal isometric contraction performed at the isokinetic dynamometer. The histogram on the left shows RTD values at 0° (RTD 0°), while the one on the right shows values of RTD at 10° plantarflexion (RTD 10°). The colours represent the Control group (blue bars), the DM group (red bars) and the DPN group (green bars). Asterisks show significant differences (p<0.05).

The analysis of peak torque values revealed a main effect for "Group" at 0° (neutral position, 0°NP) ($F_{2,51}$ =12.60, p=0.003, ηp^2=0.33) and at 10° plantarflexion (10° PF) ($F_{2,51}$ = 14.80, p<0.001, ηp^2=0.36). DPN group showed significantly lower values of maximum muscle strength (peak torque) compared to DM and Control groups at both joint ankle position 0° and 10° PF. No significant differences were found between the diabetes and the control groups (p>0.05) (Fig 29).

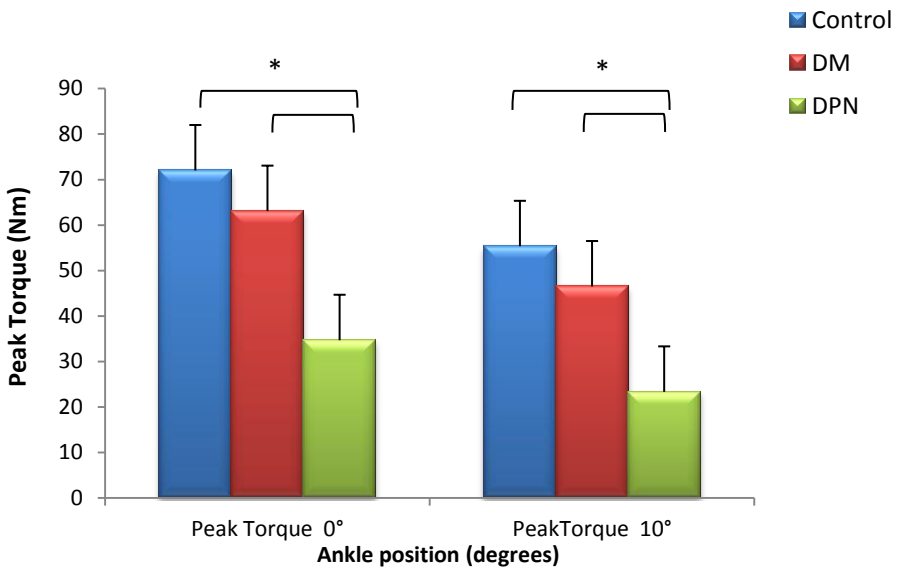


Figure 29: The histograms above display peak torque values registered during the maximal isometric strength test at the dynamometer. The histogram on the left shows peak torque values at 0° (Peak Torque 0°), while the one on the right shows values of peak torque at 10° plantarflexion (Peak Torque 10°). The colours represent the Control group (blue bars), the DM group (red bars) and the DPN group (green bars). Asterisks show significant differences ($p<0.05$).

Pearson correlation revealed different levels of correlation between rate of torque data (10° PF) and both VPT ($R = -.392$, $p=0.003$) and mNDS ($R=-.399$, $p=0.003$), as well as for peak torque values and both VPT ($R = -.611$, $p<0.001$) and mNDS ($R = -.583$, $p<0.001$) values.

7.6.3 PROPRIOCEPTION FUNCTION

A repeated measure ANOVA demonstrated a main effect for "Trials" ($F_{2,102}$ =4.92, p=0.009, ηp^2=0.88). Proprioception function increased significantly between the first trial and the third trial (Fig.30A). The percentage change between the first and the third trial were 22%, 11% and 18% for Control, DM and DPN, respectively. The control group showed the best improvement, followed by DPN, and DM

Albeit non-significant (p=0.054), the DPN group had higher proprioception "error values" (mean±SE: DPN 4.73 ± 0.66) compared to DM (3.20 ± 0.51) and Control (3.21± 0.68).

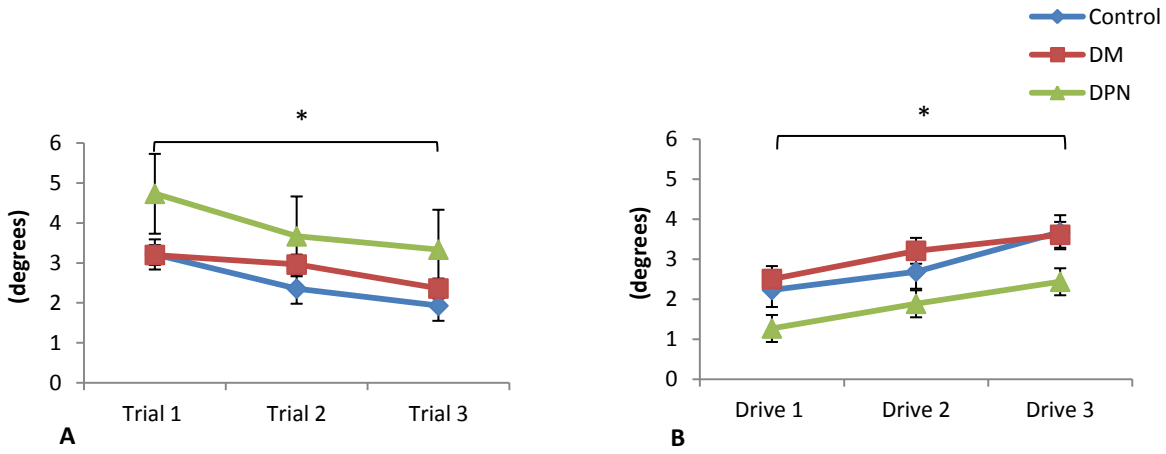


Figure 30: A) The graph on the left shows changes in the proprioception error values during a 3 trial proprioception task (Trial 1, Trial 2, Trial 3) B) The graph on the right displays the different position of the pedal (degrees) in the three drives (Drive 1, Drive 2, Drive 3). The colours represent the Control group (blue), the DM group (red) and the DPN group (green). Both pedal and proprioception values are expressed in absolute units. Asterisks show significant differences (p<0.05).

7.6.4 DRIVING SIMULATOR TASK: PEDAL CONTROL

The repeated measures ANOVA revealed a main effect for "Drives" ($F_{1,39}$ = 13.95, p=0.001, ηp^2=0.26). Mean pedal value (degrees) increased significantly across the three drives. (Fig.30B) There were no significant difference between groups (mean±SE: DPN 1.86 ± 0.77; DM 3.10 ± 0.55; Control 2.89 ± 0.71; p>0.05).

The analysis of two time periods of 3000 ms corresponding with a sharp bend, did not show any difference between pedal position (degrees) before (mean±SE: DPN -1.16 ± 0.39; DM -0.71 ± 0.32; Control -0.63± 0.41) and after (DPN -0.73 ± 0.55; DM -1.89 ± 0.46; Control -1.49 ± 0.57) that bend ($p>0.05$). At the same time, we did not find any significant different between groups (DPN-0.94 ± 0.39; DM -1.30 ± 0.32; Control -1.06 ± 0.40; $p>0.05$) (Fig.31).

The Pearson correlation coefficient between pedal position (degrees) and proprioception "error value" (degrees) was $R=-.291$ ($p<0.043$). We also observed significant correlations between pedal position (degrees) and RTD 10° ($R=.462$, $p=0.001$) and between pedal position (degrees) and peak torque 10° ($R=.492$, $p<0.001$).

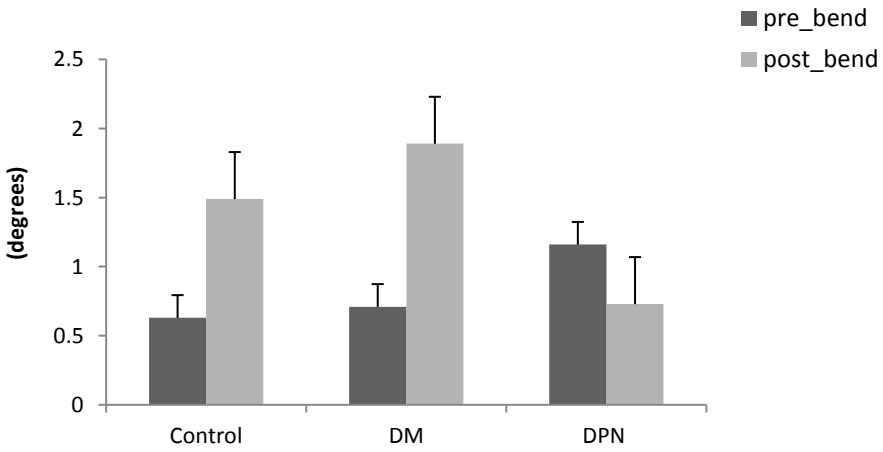


Figure 31: The graph shows the different pedal displacement (degrees) in the groups, when considering an interval of time (3000 ms.) which precede (pre-bend, in black) and follow (post-bend in grey) a sharp bend. Values are represented for each single group. Pedal values are expressed in absolute units.

7.7 DISCUSSION

Clinical manifestation associated with diabetes and diabetic peripheral neuropathy seem to have the potential for impairing driving function. The following two paragraphs will discuss the two main findings that emerge from this study on driving in people with diabetes with and without neuropathy.

Our results seem to confirm our first hypothesis of an impaired eye-steering coordination in people with diabetes. At the same time, while data on maximal strength (PT), seem to reflect the severity of the clinical manifestation associated with diabetes, we found significantly lower values of speed of strength generation (RTD) in both diabetic people with and without neuropathy compared to Controls. Pedal control measurements seem to correlate with "PT" and "RTD" and other neuropathy clinical indexes (VPT, mNDS), but no significant differences were found between groups.

7.7.1 DRIVING SIMULATOR TASK: EYE-STEERING COORDINATION

In 1938 Gibson proposed a psychophysical theory of perception for automobile driving, defining a "terrain of field of space" for the driver, with the car considered as a tool of locomotion and the driver aiming to drive in the middle of a "field of safe travel" [29]. Optic flow, one of the most important visual cues he proposed, was defined as the visual motion experienced during walking or driving [27]. Specific characteristics of this visual flow play a dominant role in the control of heading and collision detection based on visual depth, distance or orientation stimulus variables [3]. Several studies, aimed at investigating the driving performance, demonstrated that in the presence of conditions that affect the cerebellum the ability to drive decreased, attributing to it a fundamental role in controlling this motor perceptual task [224, 241, 242]. Driving implies perception and control of self-motion at greater ranges of velocity than locomotion [221]. At the same time, self-motion perception experienced by the driver depends on his own driving velocity.

The main role of the cerebellum in motor control and oculomotor coordination seems to be in part mediated by changes in retinal stimulation [224]; this evidence is supported by neurophysiological studies which have observed how the activity of some neurons in the extra-striate cortical areas were modulated by movements of the eye, the eye and head, or the hand [146]. The behaviour of a driver who looks to the inside point of a bend (tangent point) before turning the steering wheel, is considered as a motor control mechanism underlying coordinated actions. Because eyes lead, the oculomotor controller, (i.e. the collection of neural centres that together produce and control eye movements) can assist the neural system that control the steering [224]. Thus a strategy in which the eyes move with a time or phase lead over other body movements enables the oculomotor controller to assist the neural centre responsible for voluntary limb movements in various situations [224]. When this eye-steering coordination is disrupted, as a consequence of bad or late eye-movements, we observed an impaired driving performance [119, 129, 225].

We found that diabetic people showed a significantly lower eye-steering coordination compared to healthy control subjects. Scientific evidence demonstrates the same impaired behaviour during walking. Diabetic people with and without neuropathy experienced an alteration of visual perception due to a less effective visual gaze strategy: a combination of looking away from the target later and taking longer to look between targets, which leads to decreased stepping accuracy while walking [125]. During walking, the slowness in reaching the target is probably due to a difficulty in using visual information regarding a target in a feed-forward manner, as happens in groups with a high risk of falls, in contrast to younger people who generally fixate a few step ahead [5].

When looking at the time-lead values (tL), we did not find any significant differences between groups. We can assume that a minimum degree of eye-steering coordination was required in order to carry out a driving task efficiently, and it seems that the DPN required more time in order to accomplish this.

The compromise resided in the driving speed; DPN drove at the lowest velocity compared to the other groups. Diabetic patients without neuropathy, who maintain virtually the same velocity of the healthy control group, demonstrated lower eye-steering coordination values and time leads.

Comparing both drives, as velocity increases, the time lead decreases for the diabetic population, but not for the healthy control group. With a reduced time lead, help from the oculomotor controller does not arrive in time and, deprived of this assistance, steering performance suffers. This help needs to arrive in time and at the appropriate time, to steer around the corner, so that the eyes move with an optimal time lead over steering [222]. A similar adaptive mechanism to that observed in our patients with diabetic peripheral neuropathy has been observed in diabetic patients that have to negotiate a walking task around a corner. People with diabetes showed reduced velocity of gait during turning, compared to when they have to walk in a linear path [243]. It is important to note, that during natural locomotion (and driving) we tend to fixate points of the forthcoming trajectory, and the reduction of velocity could be representative of poor eye movement coordination.

In the same way, the elderly drive at slower speed in order to compensate for decreased reaction times [244, 245]. Also in this case, we can recognize a possible contribution of the cerebellum. Damage to the cerebellum has long been known to cause prolonged response latencies or reaction times. This deficit has been thought to be due to a disfacilitation of motor responses resulting from a disruption of the cerebellum function in integrating sensory information related to the spatial attribute of the target with the required motor output. We can define visual motor reaction time (RT) as the amount of time that elapses between the initiation of a visual stimulus and the completion of a motor response to that stimulus.

Reaction time is one of most important methods used to study central information processing speed and fast coordinated peripheral movement responses; when investigated through reactions to

computer simulations of changes of traffic lights, it has been shown that people with diabetes presented longer reaction times compared with healthy control subjects [246]. In the same way, the increasing motor reaction times observed in people with diabetes could also affect steering-wheel movements and consequently disrupt oculo-manual coordination.

7.7.2 NEUROMOTOR VARIABLES AND PEDAL CONTROL

Even though Gibson considered driving merely a perceptual task, it is well-established that other sensory information, such as that provided by the vestibular and proprioceptive channels, also contributes to the perception and control of self-motion [27]. The perception of his/her own movement allows the driver to make the estimation of his/her own velocity that is necessary to make provision for the time required to avoid collision and for driving safety [3]. Drivers can detect a signal and move the foot from accelerator to brake pedal in about 0.70 to 0.75 sec.; times can vary between 1.25 - 1.5 sec. in response to unexpected, but common, signals such as a lead car's brake lights [227]. In support of the previous statements, other research studies have shed light on the existence of an eye-foot coordination network controlled via feedforward mechanisms [129, 247]. This evidence made us aware of the necessity to carry out, together with oculomanual coordination data, some measurements on the car pedal. At the same time, the presence of the peripheral diabetic neuropathy makes it difficult to evaluate the contribution of visual perception to motor function impairment on the control of the pedal. So, it is therefore fundamental to take into consideration both motor reaction variables at the dynamometer, and pedal variables at the driving simulator. The action on the pedal is mostly demanded of the control of the plantar flexor muscles, and a standard emergency braking configuration could be defined as joint flexion angles of 96°, 56° and 13° for the right hip, knee and ankle respectively. On the basis of this evidence, we evaluated both strength and proprioception using a specific joint ankle angle of 10° of plantarflexion [240].

Our data demonstrated that people with diabetic peripheral neuropathy showed the lowest values of maximal strength (peak torque) compared to diabetic people without neuropathy and to healthy control subjects, between whom there were no significant differences in term of peak torque values. The literature demonstrates that neural efferent drive and contractile factors proceed in parallel; the continuous loss of motor axons, which in combination with insufficient reinnervation, results in denervation of muscles fibres, is responsible for the muscular atrophy and muscle weakness at the ankle [76]. Correspondingly atrophy of dorsal and plantar flexors was greater in patients with neuropathy than in patients without neuropathy and in healthy control subjects [90, 219]. Although, annual loss of strength of ankle dorsal and plantar flexors is more severe in neuropathic patients, annual change of muscle strength does not differ between non neuropathic diabetic patients and control subjects [94]. All things considered, our results seems to be in line with previous findings.

As regards rate of torque development (RTD), people with diabetes with and without diabetic peripheral neuropathy displayed significantly lower RTD values compared to healthy control subjects, when considering the first 150 ms of a maximal isometric contraction of the plantar flexors muscles. The rate of torque development assumes importance every time we have to exert a rapid rise in muscle force and, compared to peak torque, RTD seems to be more sensitive in detecting acute and chronic changes in neuromuscular function. Contrary to a single measure of maximal strength, speed of strength generation (RTD) is differently modulated by neural and muscular determinants, depending on their temporal occurrence and quantification [233]. In fact, motor units' discharge rate, muscle fibre types, muscle size and muscle architecture appear to influence RTD to different extents depending on the duration of the contraction [234]. For these reasons, we have to make a distinction between early phase contraction (<75 ms), where neural factors are predominant, and contraction of longer duration (>75 ms), where the RTD becomes more strongly influenced by

the speed-related properties of the muscles (% type II fibres) and maximal strength values per se [248]. In this case, the slower speed of strength generation observed in the diabetic population with and without neuropathy compared to healthy control groups could be in part explained by the fact that fast-twitch glycolytic fibres (type II fibres) are more vulnerable than slow-twitch oxidative fibres under a variety of atrophic conditions related to signalling transduction, or glycaemic control [249, 250]. The reduced capability to generate adequate muscle strength in the early phase of muscle contraction could have a functional importance during driving, when we consider the safety reaction time threshold on the brake pedal to be of 0.70 sec [227]. RTD is usually used to interpret and evaluate motor outcomes because it is considered to have important functional consequences and a positive correlation with performance in daily life tasks [233]. The literature has shown that the slower strength generation observed in people with diabetes, and particularly in patients with neuropathy, can be recognized during the everyday tasks of stair ascent and stair descent. Those with diabetes but without neuropathy displayed slower ankle and knee strength generation during these tasks, but not to the same extent as the patients with moderate-severe neuropathy [125, 126].

Aware of the impaired proprioception function in the diabetic neuropathy population [214, 251], we evaluated a specific level in the functional range of motion of the dorsal and plantar flexion. In diabetic peripheral neuropathy the majority of the denervated muscle fibres are reinnervated through collateral sprouting of nearby surviving motor axons or motor end plates, resulting in the formation of very large motor units (MUs) which lead to reduced force steadiness and reduced fine motor control [90]. Surprisingly, our results demonstrated that people with peripheral neuropathy could have the potential to improving proprioception function. Although they showed the highest “error values”, their rate of improvement was similar to that observed in the diabetes and in the control groups.

When examining pedal control, in a specific time interval that precedes and follow a sharp bend, we did not find significant differences between groups but we can make an interesting observation. Despite the great variability within the same group, we noticed a completely different strategy of pedal control in patients with diabetic peripheral neuropathy compared to diabetic patients without neuropathy and to healthy control subjects. When preparing for a bend, diabetes and control groups reduced the pressure on the pedal in order to decrease velocity and immediately after the bend the pressure started to rise again. In contrast, the DPN's pedal pressure was still high when they were approaching the bend, and only in close proximity or just after the bend did the pressure start to decrease.

In support of our observations, other studies also conducted with a driving simulator have demonstrated that lower extremity sensorimotor neuropathy patients had slower mean brake response times and have an increased frequency of abnormally delayed brake reactions compared with diabetics without neuropathy and healthy control subjects [122, 123]. Recent studies showed slower brake reaction times in the diabetic population with and without neuropathy. The researchers tried to find an explanation in a commingling of different variables, such as the sensory neuropathy and inability to feel the accelerator and brake pedals, the inability to efficiently move the feet between the accelerator brake pedals and decreased visual reaction times [229]. In our study, we did not measure reaction times but the pedal position seems to be linked to the maximal strength (peak torque) that can applied on it and speed of strength generation, as well as to the severity of the manifestation associated with diabetes.

7.7.3 DRIVING SIMULATOR SICKNESS ISSUE

The literature demonstrates that people with diabetes usually present nystagmus and reduced slow scan movement of the eyes [252]. This clinical manifestation associated with diabetes could have an important role in disrupting this oculomotor coordination. Because of the connections

between the vestibular nuclei and the oculomotor system, which allow eye muscles to compensate for head movement in order to maintain stable vision in the retina, we can infer that the damage to the vestibular system may have a relevant role in controlling eye movement during driving. The mechanism of the damage to the vestibular, somatic and autonomic nervous systems has been linked to a deterioration of microcirculation associated with poor glycaemic control in diabetes. Since the vestibular apparatus in the inner ear and nerve synapses is highly vascular, the diminished supply of oxygen and nutrients would certainly decrease autonomic and somatic reflexes [253].

An impaired vestibular function could explain the motion sickness experienced in a high percentage of diabetic people with and without peripheral neuropathy. Like motion sickness, simulator sickness has been described as a syndrome because of the breadth of its symptoms, including headache, sweating, dry mouth, drowsiness, disorientation, vertigo, nausea, dizziness, and vomiting [254]. Motion sickness theory states that the symptoms are a result of conflicting visual and vestibular cues; in simulator sickness, visual motion cues are coupled with an absence of vestibular motion cues. Apart from sensory conflict theory, another interesting theory could provide us with some responses; we took into consideration the "eye movement theory" formulated by Ebenholtz [254]. This theory states that two specific eye movements, optokinetic nystagmus and vestibular ocular response, lead to motion sickness and simulator sickness [254]. According to this theory, certain stimuli can cause eye movements which create such tension in the eye muscles that they stimulate the vagus nerve, resulting in the appearance of the characteristic symptomatology.
Moreover, individual characteristics such as age, experience, gender, illness, mental rotation ability, and postural instability play key roles in inducing motion sickness, thus could explain the presentation of these symptoms also in the control group [255].

7.8 CONCLUSIONS

The use of a driving simulator for driver perception studies has become increasingly widespread in order to assess the participation and the integrity of the somatosensory system involved in this task. A reduction in eye-steering coordination was registered in the diabetic population compared to age-matched control subjects. In the same manner, diabetes seems to affect the rate of torque development, but only people diabetic peripheral neuropathy presented lower values of maximal strength. Results in eye-steering coordination demonstrated a potential impairment in driving function for diabetes patients. Conversely, many variables (rate of torque generation, peak torque, proprioception, vibration perception threshold) seem to contribute to affecting pedal control. The great variability displayed in these variables reflects the severity of a clinical manifestation of diabetes; at the same time, this makes it difficult to identify a direct link between sensorimotor function loss and a bad pedal control. We recognize the necessity to work on a more specific task in order to better discriminate the contribution of each of the variables in affecting pedal control.

Besides these findings, the reduction of driving velocity observed in people with peripheral neuropathy seems to represent the first adaptive mechanisms to solve in this population in order to enable them to undertake the task of driving efficiently.

8 OVERALL CONCLUSION

Taken together, the assessment of the role of visual information provided by optic flow stimuli in the control of stance in people with diabetic retinopathy, and the evaluation of eye movements with other motor function variables during a driving task in people with diabetic peripheral neuropathy (DPN), allow us to understand the functional importance of the sensorimotor integration process during daily life activities.

We found that retinal functionality, especially in the peripheral retina, plays a fundamental role in maintaining balance during quiet standing. We infer that postural system responses could be a direct consequence of differing retinal functionality. Cortical mechanisms based on predetermined motor action programmes seem to prevail over the sub-cortical mechanisms based on close-loop circuits. At the same time, diabetic people with and without peripheral neuropathy showed reduced eye-steering coordination and motor function. Eye-steering coordination seems to be the first parameter affecting driving function, while a reduced speed of strength generation (RTD) seems not to have a direct negative impact on the control of the pedal during driving. Furthermore, despite the severe nerve damage presented by DPN patients, we observed an improvement in the proprioception function during a three-trial session.

The results shed light on the existence of a link between visual perception and motor action. The importance of the integrity of the retina and the role of eye movements in guiding planned motor action reveals their fundamental role in affecting daily life tasks such as maintaining balance or driving a car.

References

1. Kandel E, Schwartz J, and Jessel T, *Principles of Neural Science*, ed. 4. 2014, New York: Elsevier.
2. Lappe, M., F. Bremmer, and A. Van den Berg, *Perception of self-motion from visual flow.* Trends in cognitive sciences, 1999. **3**(9): p. 329-336.
3. Gibson, J.J., *The visual perception of objective motion and subjective movement.* Psychol. Rev., 1954. **61**: p. 304-314.
4. Peterka, R.J. and M.S. Benolken, *Role of somatosensory and vestibular cues in attenuating visually induced human postural sway*. Exp Brain Res, 1995. **105**: p. 101-110.
5. Yamada, M., et al., *Maladaptive turning and gaze behavior induces impaired stepping on multiple footfall targets during gait in older individuals who are at high risk of falling.* Archives of gerontology and geriatrics, 2012. **54**(2): p. e102-e108.
6. van Asten, W.N., C.C. Gielen, and J.J. Denier van der Gon, *Postural adjustments induced by simulated motion of differently structured environments.* Exp Brain Res, 1988. **73**: p. 371-383.
7. Stoffregen, T.A., *Flow structure versus retinal location in the optical control of stance.* J Exp Psychol Hum Percept Perform, 1985. **11**: p. 554-565.
8. Peterka RJ, *Sensorimotor integration in human postural control.* J Neurophysiol 2002. **88(3)**: p. 1097–118.
9. Dijkstra, T.M., G. Schöner, and C.C. Gielen, *Temporal stability of the action-perception cycle for postural control in a moving visual environment.* Exp Brain Res, 1994. **97**: p. 477-486.
10. Lestienne, F., J. Soechting, and A. Berthoz, *Postural readjustments induced by linear motion of visual scenes.* Exp Brain Res, 1977. **28**: p. 363-384.
11. Dijkstra, T.M., et al., *Frequency dependence of the action-perception cycle for postural control in a moving visual environment: relative phase dynamics.* Biol Cybern, 1994. **71**: p. 489-501.
12. Kiemel T, Oie KS, and Jeka JJ, *Multisensory fusion and the stochastic structure of postural sway.* Biol Cybernet, 2002. **87(4)**: p. 262–77.
13. Stoffregen, T.A., *The role of optical velocity in the control of stance.* Percept Psychophys, 1986. **39**.

14. Brandt, T., J. Dichgans, and E. Koenig, *Differential effects of central versus peripheral vision on egocentric and exocentric motion perception.* . Exp Brain Res, 1973. **16**: p. 476-491.
15. Stoffregen TA, Schmuckler MA, and Gibson EJ, *Use of central and peripheral optic flow in stance and locomotion in young walkers.* Perception and Psychophysiol, 1987. **16**: p. 113–9.
16. Bronstein, A., *Suppression of visually evoked postural responses.* Experimental brain research, 1986. **63**(3): p. 655-658.
17. Lee, D. and J. Lishman, *Visual proprioceptive control of stance.* Journal of Human Movement Studies, 1975.
18. Dijkstra, T., G. Schöner, and C. Gielen, *Temporal stability of the action-perception cycle for postural control in a moving visual environment.* Experimental Brain Research, 1994. **97**(3): p. 477-486.
19. Allum JH, et al., *Differences between trunk sway characteristics on a foam support surface and on the equitest ankle-sway-referenced support surface.* Gait Posture, 2002. **16**: p. 264-270.
20. Nashner, L.M. and G. McCollum, *The organization of human postural movements: a formal basis and experimental synthesis.* Behavioral and brain sciences, 1985. **8**(01): p. 135-150.
21. Collins, J.J. and C.J. De Luca, *The effects of visual input on open-loop and closed-loop postural control mechanisms.* Exp Brain Res, 1995. **103**: p. 151-163.
22. Martin, O. and J.D. Gascuel, *Reactive Ocular and Balance Control in Immersive Visual Flows: 2D vs. 3D Virtual Stimuli.* Stud Health Technol Inform, 2009. **144**: p. 208-210.
23. Peterka, R., *Sensorimotor integration in human postural control.* Journal of neurophysiology, 2002. **88**(3): p. 1097-1118.
24. Merchant, H., A. Battaglia-Mayer, and A. Georgopoulos, *Effects of optic flow in motor cortex and area 7a.* Journal of neurophysiology, 2001. **86**(4): p. 1937-1954.
25. Pack, C. and E. Mingolla, *Global induced motion and visual stability in an optic flow illusion.* Vision Research, 1998. **38**(20): p. 3083-3093.
26. Bridgeman, B., *A review of the role of efference copy in sensory and oculomotor control systems.* Annals of biomedical engineering, 1995. **23**(4): p. 409-422.
27. Gibson, J.J., *The perception of the visual world.* Houghton Mifflin, Boston, 1950.
28. Lappe M (ed), *Neuronal processing of optic flow*. International Review of Neurobiology. Vol. 44. 2002, New York: Academic Press.

29. Gibson, J.J. and L.E. Crooks, *A theoretical field-analysis of automobile-driving.* The American journal of psychology, 1938. **51**(3): p. 453-471.
30. Raffi, M. and R.M. Siegel, *Multiple cortical representations of optic flow processing*, in *Optic flow and beyond*. 2004, Springer. p. 3-22.
31. Tong, F., *Primary visual cortex and visual awareness.* Nature Reviews Neuroscience, 2003. **4**(3): p. 219-229.
32. Lagae, L., et al., *Responses of macaque STS neurons to optic flow components: a comparison of areas MT and MST.* Journal of Neurophysiology, 1994. **71**(5): p. 1597-1626.
33. Graziano, M., R.A. Andersen, and R.J. Snowden, *Tuning of MST neurons to spiral motions.* Journal of Neuroscience, 1994. **14**(1): p. 54-67.
34. Duffy, C.J. and R.H. Wurtz, *An illusory transformation of optic flow fields.* Vision research, 1993. **33**(11): p. 1481-1490.
35. Tanaka, K., Y. Fukada, and H. Saito, *Underlying mechanisms of the response specificity of expansion/contraction and rotation cells in the dorsal part of the medial superior temporal area of the macaque monkey.* Journal of Neurophysiology, 1989. **62**(3): p. 642-656.
36. Tanaka, K. and H.-A. Saito, *Analysis of motion of the visual field by direction, expansion/contraction, and rotation cells clustered in the dorsal part of the medial superior temporal area of the macaque monkey.* Journal of neurophysiology, 1989. **62**(3): p. 626-641.
37. Schaafsma, S. and J. Duysens, *Neurons in the ventral intraparietal area of awake macaque monkey closely resemble neurons in the dorsal part of the medial superior temporal area in their responses to optic flow patterns.* Journal of Neurophysiology, 1996. **76**(6): p. 4056-4068.
38. Anderson, K.C. and R.M. Siegel, *Optic flow selectivity in the anterior superior temporal polysensory area, STPa, of the behaving monkey.* Journal of Neuroscience, 1999. **19**(7): p. 2681-2692.
39. Andersen, R.A., et al., *Multimodal representation of space in the posterior parietal cortex and its use in planning movements.* Annual review of neuroscience, 1997. **20**(1): p. 303-330.
40. Motter, B.C. and V.B. Mountcastle, *The functional properties of the light-sensitive neurons of the posterior parietal cortex studied in waking monkeys: foveal sparing and opponent vector organization.* Journal of Neuroscience, 1981. **1**(1): p. 3-26.
41. Siegel, R.M. and H.L. Read, *Models of the temporal dynamics of visual processing.* Journal of statistical physics, 1993. **70**(1): p. 297-308.

42. Marconi, B., et al., *Eye–hand coordination during reaching. I. Anatomical relationships between parietal and frontal cortex.* Cerebral Cortex, 2001. **11**(6): p. 513-527.
43. Zhang, J., et al., *Dynamics of single neuron activity in monkey primary motor cortex related to sensorimotor transformation.* Journal of Neuroscience, 1997. **17**(6): p. 2227-2246.
44. Milner, A.D., *Cerebral correlates of visual awareness.* Neuropsychologia, 1995. **33**(9): p. 1117-1130.
45. Peterka, R.J. and M.S. Benolken, *Role of somatosensory and vestibular cues in attenuating visually induced human postural sway.* Experimental Brain Research, 1995. **105**(1): p. 101-110.
46. Karlsson, A. and H. Lanshammar, *Analysis of postural sway strategies using an inverted pendulum model and force plate data.* Gait & Posture, 1997. **5**(3): p. 198-203.
47. Collins, J. and C. De Luca, *The effects of visual input on open-loop and closed-loop postural control mechanisms.* Experimental Brain Research, 1995. **103**(1): p. 151-163.
48. Boulton, A.J.M., et al., *Diabetic neuropathies: A statement by the American Diabetes Association.* Diabetes Care, 2005. **28**(4): p. 956-962.
49. Vincent, A.M., et al., *Oxidative stress in the pathogenesis of diabetic neuropathy.* Endocrine reviews, 2004. **25**(4): p. 612-628.
50. Strauss, O., *The retinal pigment epithelium in visual function.* Physiological reviews, 2005. **85**(3): p. 845-881.
51. Boulton, A.J., et al., *Diabetic somatic neuropathies.* Diabetes care, 2004. **27**(6): p. 1458-1486.
52. Taylor, H.R. and J.E. Keeffe, *World blindness: a 21st century perspective.* British Journal of Ophthalmology, 2001. **85**(3): p. 261-266.
53. Kocur, I. and S. Resnikoff, *Visual impairment and blindness in Europe and their prevention.* British Journal of Ophthalmology, 2002. **86**(7): p. 716-722.
54. Group, E.T.D.R.S.R., *Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10.* Ophthalmology, 1991. **98**(5): p. 786-806.
55. Safitri, D.W. and D. Juniati. *Classification of diabetic retinopathy using fractal dimension analysis of eye fundus image*. in *AIP Conference Proceedings*. 2017. AIP Publishing.
56. Witmer, A., et al., *Vascular endothelial growth factors and angiogenesis in eye disease.* Progress in retinal and eye research, 2003. **22**(1): p. 1-29.

57. Group, D.R.S.R., *Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8.* Ophthalmology, 1981. **88**(7): p. 583-600.
58. Prokofyeva, E. and E. Zrenner, *Epidemiology of major eye diseases leading to blindness in Europe: a literature review.* Ophthalmic research, 2012. **47**(4): p. 171-188.
59. Murphy, R., *Management of diabetic retinopathy.* American family physician, 1995. **51**(4): p. 785-796.
60. Fong, D.S., et al., *Retinopathy in diabetes.* Diabetes care, 2004. **27**(suppl 1): p. s84-s87.
61. Antonetti, D.A., et al., *Diabetic retinopathy.* Diabetes, 2006. **55**(9): p. 2401-2411.
62. Boulton, M. and P. Dayhaw-Barker, *The role of the retinal pigment epithelium: topographical variation and ageing changes.* Eye, 2001. **15**(3): p. 384-389.
63. Simó, R. and C. Hernández, *Neurodegeneration in the diabetic eye: new insights and therapeutic perspectives.* Trends in Endocrinology & Metabolism, 2014. **25**(1): p. 23-33.
64. Bresnick, G.H. and M. Palta, *Predicting progression to severe proliferative diabetic retinopathy.* Archives of Ophthalmology, 1987. **105**(6): p. 810-814.
65. Williams, G.A., et al., *Single-field fundus photography for diabetic retinopathy screening: a report by the American Academy of Ophthalmology.* Ophthalmology, 2004. **111**(5): p. 1055-1062.
66. Bengtsson, B., A. Heijl, and E. Agardh, *Visual fields correlate better than visual acuity to severity of diabetic retinopathy.* Diabetologia, 2005. **48**(12): p. 2494-2500.
67. Subash, M., et al., *The effect of multispot laser panretinal photocoagulation on retinal sensitivity and driving eligibility in patients with diabetic retinopathy.* JAMA ophthalmology, 2016. **134**(6): p. 666-672.
68. Group, D.R.S.R., *Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings.* Ophthalmology, 1978. **85**: p. 82-106.
69. Simó, R., et al., *Angiogenic and antiangiogenic factors in proliferative diabetic retinopathy.* Current diabetes reviews, 2006. **2**(1): p. 71-98.
70. Shrestha, G.S. and R. Kaiti, *Visual functions and disability in diabetic retinopathy patients.* Journal of optometry, 2014. **7**(1): p. 37-43.
71. Cooke, J.B. and A.L. Cochrane, *A practical guide to low vision management of patients with diabetes.* Clinical and Experimental Optometry, 2001. **84**(3): p. 155-161.

72. Szlyk, J.P., et al., *Relationship of retinal structural and clinical vision parameters to driving performance of diabetic retinopathy patients.* Journal of rehabilitation research and development, 2004. **41**(3): p. 347.
73. Neubauer, A.S. and M.W. Ulbig, *Laser treatment in diabetic retinopathy.* Ophthalmologica, 2007. **221**(2): p. 95-102.
74. Thomas, P., *Classification, differential diagnosis, and staging of diabetic peripheral neuropathy.* Diabetes, 1997. **46**(Supplement 2): p. S54-S57.
75. Young, M.J., et al., *Osteopenia, neurological dysfunction, and the development of Charcot neuroarthropathy.* Diabetes Care, 1995. **18**(1): p. 34-38.
76. Andreassen, C.S., J.K. Jakobsen, and H. Andersen, *Muscle weakness in diabetic patients with neuropathy-a progressive disorder.* Diabetes, 2006(55): p. 806-812.
77. Said, G., *Diabetic neuropathy--a review.* Nature Reviews. Neurology, 2007. **3**(6): p. 331.
78. King, R., *The role of glycation in the pathogenesis of diabetic polyneuropathy.* Molecular Pathology, 2001. **54**(6): p. 400.
79. Schaumburg, H.H. and P.S. Spencer, *Clinical and experimental studies of distal axonopathy—a frequent form of brain and nerve damage produced by environmental chemical hazards.* Annals of the New York Academy of Sciences, 1979. **329**(1): p. 14-29.
80. Mendez, J., *Advanced glycosylation end products and chronic complications of diabetes mellitus.* Gaceta medica de Mexico, 2002. **139**(1): p. 49-55.
81. Dyck, P.J., L.J. Melton, and P.C. O'brien, *Approaches to improve epidemiological studies of diabetic neuropathy: insights from the Rochester Diabetic Neuropathy Study.* Diabetes, 1997. **46**(Supplement 2): p. S5-S8.
82. Dyck, P.J., et al., *The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort The Rochester Diabetic Neuropathy Study.* Neurology, 1993. **43**(4): p. 817-817.
83. Abbott, C., et al., *The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort.* Diabetic medicine, 2002. **19**(5): p. 377-384.
84. Donaghy, A., et al., *Accuracy of Clinical Techniques for Evaluating Lower Limb Sensorimotor Functions Associated With Increased Fall Risk.* PM and R, 2016. **8**(4): p. 331-339.

85. Mayfield, J.A. and J.R. Sugarman, *The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes.* Journal of Family Practice, 2000. **49**(11): p. S17-S17.
86. Vaz, M.M., et al., *Postural control and functional strength in patients with type 2 diabetes mellitus with and without peripheral neuropathy.* Archives of Physical Medicine and Rehabilitation, 2013. **94**(12): p. 2465-2470.
87. Chiles, N.S., et al., *Diabetes, peripheral neuropathy, and lower-extremity function.* Journal of diabetes and its complications, 2014. **28**(1): p. 91-95.
88. Sénéchal, M., et al., *Association between changes in muscle quality with exercise training and changes in cardiorespiratory fitness measures in individuals with type 2 diabetes mellitus: Results from the HART-D study.* PloS one, 2015. **10**(8): p. e0135057.
89. Shun, C.T., et al., *Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments.* Brain, 2004. **127**(7): p. 1593-1605.
90. Andreassen, C.S., et al., *Accelerated atrophy of lower leg and foot muscles—a follow-up study of long-term diabetic polyneuropathy using magnetic resonance imaging (MRI).* Diabetologia, 2009. **52**(6): p. 1182-1191.
91. Simoneau, G.G., et al., *Role of somatosensory input in the control of human posture.* Gait & posture, 1995. **3**(3): p. 115-122.
92. Uccioli, L., et al., *Contribution of central neuropathy to postural instability in IDDM patients with peripheral neuropathy.* Diabetes Care, 1997. **20**(6): p. 929-934.
93. Simoneau, G.G., et al., *Postural instability in patients with diabetic sensory neuropathy.* Diabetes Care, 1994. **17**(12): p. 1411-1421.
94. Andersen, H., *Motor dysfunction in diabetes.* Diabetes/metabolism research and reviews, 2012. **28**(S1): p. 89-92.
95. Andersen, H. and P. Mogensen, *Disordered Mobility of Large Joints in Association with Neuropathy in Patients with Long-standing Insulin-dependent Diabetes Mellitus.* Diabetic medicine, 1997. **14**(3): p. 221-227.
96. Cavanagh, P., et al., *Problems with Gait and Posture in Neuropathic Patients with Insulin-Dependent Diabetes Mellitus.* Diabetic Medicine, 1992. **9**(5): p. 469-474.
97. Gibson, J.J., *The perception of the visual world*. 1950, Boston: Houghton Mifflin.
98. Paulus, W., A. Straube, and T. Brandt, *Visual stabilization of posture: physiological stimulus characteristics and clinical aspects.* Brain, 1984. **107**(4): p. 1143-1163.

99. Paulus WM, Straube A, and Brandt T, *Visual stabilization of posture. Physiological stimulus characteristics and clinical aspects* Brain, 1984. **107**: p. 1143-1163.
100. Mahboobin, A., et al., *Sensory re-weighting in human postural control during moving-scene perturbations.* Experimental Brain Research, 2005. **167**(2): p. 260-267.
101. Zupan, L.H., D.M. Merfeld, and C. Darlot, *Using sensory weighting to model the influence of canal, otolith and visual cues on spatial orientation and eye movements.* Biological cybernetics, 2002. **86**(3): p. 209-230.
102. Simoneau, G.G., et al., *Diabetic sensory neuropathy effect on ankle joint movement perception.* Archives of physical medicine and rehabilitation, 1996. **77**(5): p. 453-460.
103. Barber, A.J., *A new view of diabetic retinopathy: a neurodegenerative disease of the eye.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2003. **27**(2): p. 283-290.
104. Grewal, G.S., et al., *Sensor-Based Interactive Balance Training with Visual Joint Movement Feedback for Improving Postural Stability in Diabetics with Peripheral Neuropathy: A Randomized Controlled Trial.* Gerontology, 2015. **61**(6): p. 567-574.
105. Ghanavati, T., et al., *Functional balance in elderly with diabetic neuropathy.* Diabetes research and clinical practice, 2012. **96**(1): p. 24-28.
106. Nardone, A., M. Grasso, and M. Schieppati, *Balance control in peripheral neuropathy: Are patients equally unstable under static and dynamic conditions?* Gait and Posture, 2006. **23**(3): p. 364-373.
107. Roman de Mettelinge, T., et al., *Understanding the Relationship between Type 2 Diabetes Mellitus and Falls in Older Adults: A Prospective Cohort Study.* PLoS ONE, 2013. **8**(6).
108. van der Kooij, H., et al., *A multisensory integration model of human stance control.* Biological cybernetics, 1999. **80**(5): p. 299-308.
109. Siegler, I., et al. *Sensorimotor integration in a driving simulator: contributions of motion cueing in elementary driving tasks*. in *Proceedings of Driving Simulation Conference*. 2001.
110. Boucher, P., et al., *Postural stability in diabetic polyneuropathy.* Diabetes Care, 1995. **18**(5): p. 638-645.
111. Di Nardo, W., et al., *The use of dynamic posturography to detect neurosensorial disorder in IDDM without clinical neuropathy.* Journal of Diabetes and its Complications, 1999. **13**(2): p. 79-85.
112. Simmons, R.W. and C. Richardson, *The effects of muscle activation on postural stability in diabetes mellitus patients with cutaneous sensory deficit in the foot.* Diabetes Research and Clinical Practice, 2001. **53**(1): p. 25-32.

113. Centomo, H., et al., *Postural control following a self-initiated reaching task in type 2 diabetic patients and age-matched controls.* Gait & posture, 2007. **25**(4): p. 509-514.
114. Greenbaum, D., et al., *Pathological observations in 6 cases of diabetic neuropathy.* Brain, 1964. **87**: p. 201-214.
115. Mimori, Y., et al., *Statokinesigram of patients with diabetic neuropathy*, in *Diabetic neuropathy: Proceedings of the International Symposium in Diabetic Neuropathy* G.Y. Horiuchi and A. Kogurek, Editors. 1982, Excerpta Medica: New York. p. 168-172.
116. Van Deursen, R.W. and G.G. Simoneau, *Foot and ankle sensory neuropathy, proprioception, and postural stability.* Journal of Orthopaedic and Sports Physical Therapy, 1999. **29**: p. 718-726.
117. Horak, F.B., *Postural ataxia related to somatosensory loss*, in *Gait disorders: Advances in neurology* R. E., M. Hallett, and J. Jankovix, Editors. 2001, Lippincott Williams & Wilkins: Philadelphia. p. 173-182.
118. Abdul Razzak, R. and W. Hussein, *Postural visual dependence in asymptomatic type 2 diabetic patients without peripheral neuropathy during a postural challenging task.* Journal of Diabetes and its Complications, 2016. **30**(3): p. 501-506.
119. Marple-Horvat, D., et al., *Prevention of coordinated eye movements and steering impairs driving performance.* Experimental brain research, 2005. **163**(4): p. 411-420.
120. Wilson, M., M. Chattington, and D.E. Marple-Horvat, *Eye movements drive steering: Reduced eye movement distribution impairs steering and driving performance.* Journal of motor behavior, 2008. **40**(3): p. 190-202.
121. Wilson, M., et al., *Eye movements coordinated with steering benefit performance even when vision is denied.* Experimental brain research, 2007. **176**(3): p. 397-412.
122. Spiess, K.E., L.E. Sansosti, and A.J. Meyr, *Diabetic driving studies—part 2: a comparison of brake response time between drivers with diabetes with and without lower extremity sensorimotor neuropathy.* The Journal of Foot and Ankle Surgery, 2017. **56**(3): p. 573-576.
123. Meyr, A.J. and K.E. Spiess, *Diabetic driving studies—part 1: brake response time in diabetic drivers with lower extremity neuropathy.* The Journal of Foot and Ankle Surgery, 2017. **56**(3): p. 568-572.
124. Brown, S.J., et al., *Altered joint moment strategy during stair walking in diabetes patients with and without peripheral neuropathy.* Gait & posture, 2016. **46**: p. 188-193.

125. Handsaker, J., et al., *People with diabetic peripheral neuropathy display a decreased stepping accuracy during walking: potential implications for risk of tripping.* Diabetic Medicine, 2015.
126. Handsaker, J.C., et al., *Contributory factors to unsteadiness during walking up and down stairs in patients with diabetic peripheral neuropathy.* Diabetes care, 2014. **37**(11): p. 3047-3053.
127. Reeves, N.D., et al., *Aging and type 2 diabetes: consequences for motor control, musculoskeletal function, and whole-body movement.* Journal of aging research, 2013. **2013**.
128. Wild, D., et al., *A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education.* Patient education and counseling, 2007. **68**(1): p. 10-15.
129. Hollands, M.A. and D.E. Marple-Horvat, *Coordination of eye and leg movements during visually guided stepping.* Journal of motor behavior, 2001. **33**(2): p. 205-216.
130. Winter, D.A., *Human balance and posture control during standing and walking.* Gait & Posture, 1995. **3**: p. 193-214.
131. Nashner, L.M., *Adapting reflexes controlling the human posture.* Exp Brain Res, 1976. **26**: p. 59-72.
132. Schöner, G., *Dynamic theory of action-perception patterns: the "moving room" paradigm.* Biol Cybern, 1991. **64**: p. 455-462.
133. Accornero, N., et al., *Clinical multisegmental posturography: age-related changes in stance control.* Electroencephalogr Clin Neurophysiol, 1997. **105**: p. 213-219.
134. Fitzpatrick, R., D.K. Rogers, and D.I. McCloskey, *Stable human standing with lower-limb muscle afferents providing the only sensory input.* J Physiol, 1994. **480**: p. 395-403.
135. Edwards AS, *Body sway and vision.* J Exp. Psychol., 1946 **36**: p. 526-535.
136. Lord SR, *Visual risk factors for falls in older people.* Age Ageing, 2006. **35**: p. ii42–ii45.
137. Lee, D. and J.R. Lishman, *Visual proprioceptive control of stance.* Journal of Human Movement Studies, 1975. **1**: p. 87-95.
138. Gibson, J.J., *Visually controlled locomotion and visual orientation in animals.* Br J Psychol 1958. **49**: p. 182-194.
139. Lee DN and Aronson E, *Visual proprioceptive control of standing in human infants.* Percept Psychophys, 1974. **15**: p. 529–532.
140. Lee, D.N. and R. Lishman, *Visual control of locomotion.* Scandinavian journal of psychology, 1977. **18**(1): p. 224-230.

141. Persiani, M., et al., *Laterality of stance during optic flow stimulation in male and female young adults.* BioMed research international, 2015. **2015**.
142. Amblard, B. and A. Carblanc, *Role of foveal and peripheral visual information in maintenance of postural equilibrium in man.* Perceptual and Motor Skills, 1980. **51**(3): p. 903-912.
143. Straube, A., et al., *Dependence of visual stabilization of postural sway on the cortical magnification factor of restricted visual fields.* Experimental brain research, 1994. **99**(3): p. 501-506.
144. Fahle, M. and C. Wehrhahn, *Motion perception in the peripheral visual field.* Graefe's archive for clinical and experimental ophthalmology, 1991. **229**(5): p. 430-436.
145. Stoffregen, T.A., *Flow structure versus retinal location in the optical control of stance.* Journal of Experimental Psychology: Human Perception and Performance, 1985. **11**(5): p. 554.
146. Layton, O.W. and N.A. Browning, *A unified model of heading and path perception in primate MSTd.* PLoS computational biology, 2014. **10**(2): p. e1003476.
147. Warren, W.H. and D.J. Hannon, *Eye movements and optical flow.* JOSA A, 1990. **7**(1): p. 160-169.
148. Nougier, V., et al., *Contribution of central and peripheral vision to the regulation of stance: developmental aspects.* Journal of experimental child psychology, 1998. **68**(3): p. 202-215.
149. Van Asten, W., C. Gielen, and J.D. Van Der Gon, *Postural adjustments induced by simulated motion of differently structured environments.* Experimental Brain Research, 1988. **73**(2): p. 371-383.
150. Stoffregen, T.A., et al., *Modulating postural control to facilitate visual performance.* Human Movement Science, 2000. **19**(2): p. 203-220.
151. Piponnier, J.-C., J.-M. Hanssens, and J. Faubert, *Effect of visual field locus and oscillation frequencies on posture control in an ecological environment.* Journal of Vision, 2009. **9**(1): p. 13-13.
152. Piponnier, J.C., J.M. Hanssens, and J. Faubert, *Effect of visual field locus and oscillation frequencies on posture control in an ecological environment.* J Vis, 2009. **9**: p. 13.1-10.
153. Baratto, L., et al., *A new look at posturographic analysis in the clinical context: sway-density versus other parameterization techniques.* Motor control, 2002. **6**(3): p. 246-270.
154. Palmieri, R.M., et al., *Center-of-pressure parameters used in the assessment of postural control.* Journal of Sport Rehabilitation, 2002. **11**(1): p. 51-66.

155. Reaz, M.B., M. Hussain, and F. Mohd-Yasin, *Techniques of EMG signal analysis: detection, processing, classification and applications.* Biological procedures online, 2006. **8**(1): p. 11-35.

156. Basmajian JV and De Luca CJ, *Muscles alive: their functions revealed by electromyography*. Vol. 5. 1985, Baltimore: MD: Williams and Wilkins.

157. Loram ID, Maganaris CN, and Lakie M, *Paradoxical muscle movement in human standing.* J Physiol 2004. **556**: p. 683-689.

158. Nashner L and McCollum G, *The organization of human postural movements: A formal basis and experimental synthesis.* The Behavioral and Brain Sciences, 1985. **8,**: p. 135-172.

159. Horak FB and Nashner LM, *Central programming of postural movements: Adaptation to altered support-surface configurations.* Journal of Neurophysiology, 1986. **55**: p. 1369-1381.

160. Maurer C, et al., *Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease.* Brain, 2003. **126**: p. 1146-1163.

161. Horak FB and Macpherson JM, *Postural orientation and equilibrium*, in *Handbook of Physiology*, Rowell L and Shepherd J, Editors. 1996, Oxford University Press: New York. p. 225-292.

162. Pozzo T, Berthoz A, and Lefort L, *Head stabilization during various locomotor tasks in humans. 1. Normal subjects.* Exp Brain Res, 1990. **82(1)**: p. 97–106.

163. Assaiante C and Amblard B, *An ontogenetic model of sensorimotor organization of balance control in humans.* Human Movement Science, 1995. **14**: p. 13-43.

164. Bronstein AM, *Evidence for a vestibular input contributing to dynamic head stabilization in man.* Acta Oto-Laryngologica, 1988. **105**: p. 1-6.

165. Mizrahi, J. and Z. Susak, *Bi-lateral reactive force patterns in postural sway activity of normal subjects.* Biological cybernetics, 1989. **60**(4): p. 297-305.

166. Kinsella-Shaw, J.M., et al., *Laterality of quiet standing in old and young.* Experimental brain research, 2013. **231**(4): p. 383-396.

167. Aruin A, Ota T, and Latash ML, *Anticipatory postural adjustments associated with lateral and rotational perturbations during standing.* J. Electromyogr. Kinesiol. , 2001. **11**: p. 39-51.

168. Fitzpatrick, R., D. Burke, and S.C. Gandevia, *Loop gain of reflexes controlling human standing measured with the use of postural and vestibular disturbances.* J Neurophysiol, 1996. **76**: p. 3994-4008.

169. Collins, J.J. and D.L. C.J., *Open-loop and closed-loop control of posture: A random-walk analysis of center-of-pressure trajectories.* Exp Brain Res, 1993. **95**: p. 308-318.
170. Riccio, G.E. and V. McDonald, *Methods for investigating adaptive postural control.* Proc Satellite Meet Soc Neurosci, 1998. **Nov**: p. 6–7.
171. Gatev, P., et al., *Feedforward ankle strategy of balance during quiet stance in adults.* J Physiol, 1999. **514**: p. 915–928
172. Raffi, M., et al., *Importance of optic flow for postural stability of male and female young adults.* European journal of applied physiology, 2014. **114**(1): p. 71-83.
173. Elias, L.J., M.P. Bryden, and M.B. Bulman-Fleming, *Footedness is a better predictor than is handedness of emotional lateralization.* Neuropsychologia, 1998. **36**: p. 37-43.
174. Levin, H.S., et al., *Dichotic listening and manual performance in relation to magnetic resonance imaging after closed head injury.* Journal of Neurol, Neurosurg Psychiatry, 1989. **52**: p. 1162-1169.
175. Raffi, M., et al., *Importance of optic flow for postural stability of male and female young adults.* Eur J Appl Physiol, 2014. **114**: p. 71-83.
176. Rocchi, L., L. Chiari, and A. Cappello, *Feature selection of stabilometric parameters based on principal component analysis.* Med. Biol. Eng. Comput., 2004. **42**: p. 71-79.
177. Kapteyn TS, et al., *Standaxdization in platform stabilometry being a part of posmrography.* Agressologie, 1983. **24**: p. 321-326.
178. Harris GF, et al., *Standing Postural Stability Assessment and Signal Stationarity in Children with Cerebral Palsy.* IEEE Transactions on Rehabilitation Engineering, 1993. **1(1)**: p. 35-42.
179. Raez MBI, Hussain MS, and Mohd-Yasin F, *Techniques of EMG signal analysis: Detection, processing, classification and applications.* Biological Procedures Online, 2006. **8**: p. 11-35.
180. Regan, D. and K. Beverley, *How do we avoid confounding the direction we are looking and the direction we are moving?* Science, 1982. **215**(4529): p. 194-196.
181. Raffi, M., et al., *Angle of gaze and optic flow direction modulate body sway.* Journal of Electromyography and Kinesiology, 2017.
182. Mishkin, M. and L.G. Ungerleider, *Contribution of striate inputs to the visuospatial functions of parietopreoccipital cortex in monkeys.* Behav Brain Res, 1982. **6**: p. 57-77.
183. Osterberg G, *opography of the layer of rods and cones in the human retina.* T Acta ophthal, 1935. **13 (suppi.)(6)**: p. 11-97.

184. Raffi, M. and R.M. Siegel, *Functional architecture of spatial attention in the parietal cortex of the behaving monkey.* J Neurosci, 2005. **25**: p. 5171-5186.
185. Siegel, R.M., et al., *Functional architecture of eye position gain fields in visual association cortex of behaving monkey.* J. Neurophysiol, 2003. **90**: p. 1279-1294.
186. Winter, D.A., et al., *Motor mechanisms of balance during quiet standing.* J Electromyogr Kinesiol, 2003. **13**: p. 49-56.
187. Wang Z and Newell KM, *Asymmetry of foot position and weight distribution channels the inter-leg coordination dynamics of standing.* Exp Brain Res, 2012. **222**: p. 333-344.
188. Kim, G.T., M. Ferdjallah, and G.F. Harris, *Fast Computational Analysis of Sway Area Using Center of Pressure Data in Normal Children and Children with Cerebral Palsy.* American Journal of Biomedical Sciences, 2009. **1(4)**: p. 364-372.
189. Palmieri, R.M., et al., *Center-of-Pressure Parameters Used in the Assessment of Postural Control.* J Sport Rehabil, 2002. **11**: p. 51-66.
190. Anker, L.C., et al., *The relation between postural stability and weight distribution in healthy subjects.* Gait & Posture, 2008. **27**: p. 471-477.
191. Runge, C., et al., *Ankle and hip postural strategies defined by joint torques.* Gait & posture, 1999. **10**(2): p. 161-170.
192. Colobert, B., et al., *Force-plate based computation of ankle and hip strategies from double-inverted pendulum model.* Clinical biomechanics, 2006. **21**(4): p. 427-434.
193. Pahor, D., *Visual field loss after argon laser panretinal photocoagulation in diabetic retinopathy: full-versus mild-scatter coagulation.* International ophthalmology, 1998. **22**(5): p. 313-319.
194. Berencsi, A., M. Ishihara, and K. Imanaka, *The functional role of central and peripheral vision in the control of posture.* Human movement science, 2005. **24**(5): p. 689-709.
195. Anand, V., et al., *Postural stability in the elderly during sensory perturbations and dual tasking: The influence of refractive blur.* Investigative Ophthalmology and Visual Science, 2003. **44**(7): p. 2885-2891.
196. Perrin, P.P., et al., *Influence of visual control, conduction, and central integration on static and dynamic balance in healthy older adults.* Gerontology, 1997. **43**(4): p. 223-231.
197. Hanssens, J.-M., et al., *Visually induced postural reactivity is velocity-dependent at low temporal frequencies and frequency-dependent at high temporal frequencies.* Experimental brain research, 2013. **229**(1): p. 75-84.

198. Rocchi, L., L. Chiari, and A. Cappello, *Feature selection of stabilometric parameters based on principal component analysis.* Medical and Biological Engineering and Computing, 2004. **42**(1): p. 71-79.
199. Herrera-Rangel, A., et al., *The influence of peripheral neuropathy, gender, and obesity on the postural stability of patients with type 2 diabetes mellitus.* Journal of Diabetes Research, 2014. **2014**.
200. Lim, K.B., et al., *Comparison of balance ability between patients with type 2 diabetes and with and without peripheral neuropathy.* PM and R, 2014. **6**(3): p. 209-214.
201. Kandel, E.R., et al., *Principles of neural science*. Vol. 4. 2000: McGraw-hill New York.
202. Muir, J.W., et al., *Dynamic parameters of balance which correlate to elderly persons with a history of falls.* Plos one, 2013. **8**(8): p. e70566.
203. Pizzigalli, L., et al., *The contribution of postural balance analysis in older adult fallers: A narrative review*. Journal of bodywork and movement therapies, 2016. **20**(2): p. 409-417.
204. Prado, J.M., T.A. Stoffregen, and M. Duarte, *Postural sway during dual tasks in young and elderly adults.* Gerontology, 2007. **53**(5): p. 274-281.
205. Dokka, K., R.V. Kenyon, and E.A. Keshner, *Influence of visual scene velocity on segmental kinematics during stance.* Gait & posture, 2009. **30**(2): p. 211-216.
206. Jeka, J., et al., *Controlling human upright posture: velocity information is more accurate than position or acceleration.* Journal of neurophysiology, 2004. **92**(4): p. 2368-2379.
207. Cornilleau-Pérès, V., et al., *Measurement of the visual contribution to postural steadiness from the COP movement: methodology and reliability.* Gait & posture, 2005. **22**(2): p. 96-106.
208. Fulk, G.D., et al., *The effects of diabetes and/or peripheral neuropathy in detecting short postural perturbations in mature adults.* Journal of NeuroEngineering and Rehabilitation, 2010. **7**(1).
209. Lord, S., et al., *Sensori-motor Function in Older Persons with Diabetes.* Diabetic medicine, 1993. **10**(7): p. 614-618.
210. Baumberger, B., B. Isableu, and M. Flückiger, *The visual control of stability in children and adults: postural readjustments in a ground optical flow.* Experimental brain research, 2004. **159**(1): p. 33-46.
211. Brandt, T., et al., *Visual-Vestibular and Visuovisual Cortical Interaction.* Annals of the New York Academy of Sciences, 2002. **956**(1): p. 230-241.

212. Laughton, C.A., et al., *Aging, muscle activity, and balance control: physiologic changes associated with balance impairment.* Gait & posture, 2003. **18**(2): p. 101-108.
213. Morasso PG, et al., *Internal models in the control of posture.* Neural Networks 1999. **12**: p. 1173-1180.
214. Van Deursen, R. and G.G. Simoneau, *Foot and ankle sensory neuropathy, proprioception, and postural stability.* Journal of orthopaedic & sports physical therapy, 1999. **29**(12): p. 718-726.
215. Brugnoni, G. and D. Alpini, *Medicina fisica e riabilitativa nei disturbi di equilibrio*. 2007: Springer.
216. Sartor, C.D., et al., *Effects of a combined strengthening, stretching and functional training program versus usual-care on gait biomechanics and foot function for diabetic neuropathy: a randomized controlled trial.* BMC musculoskeletal disorders, 2012. **13**(1): p. 36.
217. Uccioli, L., et al., *Body sway in diabetic neuropathy.* Diabetes care, 1995. **18**(3): p. 339-344.
218. Andersen, H., et al., *Muscular atrophy in diabetic neuropathy: a stereological magnetic resonance imaging study.* Diabetologia, 1997. **40**(9): p. 1062-1069.
219. Bus, S.A., et al., *Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot a magnetic resonance imaging study.* Diabetes Care, 2002. **25**(8): p. 1444-1450.
220. Petrofsky, J., S. Lee, and S. Bweir, *Gait characteristics in people with type 2 diabetes mellitus.* European Journal of Applied Physiology, 2005. **93**(5-6): p. 640-647.
221. Kemeny, A. and F. Panerai, *Evaluating perception in driving simulation experiments.* Trends in cognitive sciences, 2003. **7**(1): p. 31-37.
222. Chattington, M., et al., *Eye–steering coordination in natural driving.* Experimental brain research, 2007. **180**(1): p. 1-14.
223. Land, M.F. and D.N. Lee, *Where we look when we steer.* Nature, 1994. **369**(6483): p. 742-744.
224. Miall, R. and G. Reckess, *The cerebellum and the timing of coordinated eye and hand tracking.* Brain and cognition, 2002. **48**(1): p. 212-226.
225. Crowdy, K., et al., *Rehearsal by eye movement improves visuomotor performance in cerebellar patients.* Experimental brain research, 2002. **146**(2): p. 244-247.
226. Kumar, A.N., et al., *Tests of models for saccade–vergence interaction using novel stimulus conditions.* Biological cybernetics, 2006. **95**(2): p. 143-157.
227. Green, M., *" How long does it take to stop?" Methodological analysis of driver perception-brake times.* Transportation human factors, 2000. **2**(3): p. 195-216.

228. Jeng, C.L., et al., *Driving brake reaction time following right ankle arthrodesis.* Foot & ankle international, 2011. **32**(9): p. 896-899.
229. Sansosti, L.E., K.E. Spiess, and A.J. Meyr, *Diabetic driving studies—part 3: a comparison of mean brake response time between neuropathic diabetic drivers with and without foot pathology.* The Journal of Foot and Ankle Surgery, 2017. **56**(3): p. 577-580.
230. Behr, M., et al., *Posture and muscular behaviour in emergency braking: An experimental approach.* Accident Analysis & Prevention, 2010. **42**(3): p. 797-801.
231. Özdirenç, M., S. Biberoğlu, and A. Özcan, *Evaluation of physical fitness in patients with type 2 diabetes mellitus.* Diabetes research and clinical practice, 2003. **60**(3): p. 171-176.
232. Lacherez, P., et al., *Sensorimotor and postural control factors associated with driving safety in a community-dwelling older driver population.* Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 2014. **69 A**(2): p. 240-244.
233. Maffiuletti, N.A., *Physiological and methodological considerations for the use of neuromuscular electrical stimulation.* European journal of applied physiology, 2010. **110**(2): p. 223-234.
234. Andersen, L.L. and P. Aagaard, *Influence of maximal muscle strength and intrinsic muscle contractile properties on contractile rate of force development.* European journal of applied physiology, 2006. **96**(1): p. 46-52.
235. Partanen, J., et al., *Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus.* New England Journal of Medicine, 1995. **333**(2): p. 89-94.
236. McGraw, P., B. Winn, and D. Whitaker, *Reliability of the Snellen chart.* BMJ: British Medical Journal, 1995. **310**(6993): p. 1481.
237. LaRoche, D.P., et al., *Rapid torque development in older female fallers and nonfallers: A comparison across lower-extremity muscles.* Journal of Electromyography and Kinesiology, 2010. **20**(3): p. 482-488.
238. Aagaard, P., et al., *Mechanical muscle function, morphology, and fiber type in lifelong trained elderly.* Medicine and science in sports and exercise, 2007. **39**(11): p. 1989-1996.
239. Ema, R., et al., *Association between rapid force production by the plantar flexors and balance performance in elderly men and women.* Age, 2016. **38**(5-6): p. 475-483.
240. Palmertz, C., L. Jakobsson, and A.-S. Karlsson. *Pedal use and foot positioning during emergency braking*. in *IRCOBI Conference on the Biomechanics of Impact*. 1998.

241. van Donkelaar, P. and R.G. Lee, *Interactions between the eye and hand motor systems: disruptions due to cerebellar dysfunction.* Journal of Neurophysiology, 1994. **72**(4): p. 1674-1685.

242. Marple-Horvat, D.E., et al., *Alcohol badly affects eye movements linked to steering, providing for automatic in-car detection of drink driving.* Neuropsychopharmacology, 2008. **33**(4): p. 849-858.

243. Mueller, M.J., et al., *Differences in the gait characteristics of patients with diabetes and peripheral neuropathy compared with age-matched controls.* Physical therapy, 1994. **74**(4): p. 299-308.

244. Molnar, F.J., et al., *Acceptability and concurrent validity of measures to predict older driver involvement in motor vehicle crashes: An Emergency Department pilot case-control study.* Accident Analysis and Prevention, 2007. **39**(5): p. 1056-1063.

245. Molnar, L.J. and D.W. Eby, *The relationship between self-regulation and driving-related abilities in older drivers: an exploratory study.* Traffic injury prevention, 2008. **9**(4): p. 314-319.

246. Sanchez-Marin, F.J. and J.A. Padilla-Medina, *Simple reaction times and performance in the detection of visual stimuli of patients with diabetes.* Computers in biology and medicine, 2010. **40**(6): p. 591-596.

247. Hollands, M.A., N.V. Ziavra, and A.M. Bronstein, *A new paradigm to investigate the roles of head and eye movements in the coordination of whole-body movements.* Experimental brain research, 2004. **154**(2): p. 261-266.

248. Folland, J., M. Buckthorpe, and R. Hannah, *Human capacity for explosive force production: neural and contractile determinants.* Scandinavian journal of medicine & science in sports, 2014. **24**(6): p. 894-906.

249. Tracy, B.L. and R.M. Enoka, *Older adults are less steady during submaximal isometric contractions with the knee extensor muscles.* Journal of Applied Physiology, 2002. **92**(3): p. 1004-1012.

250. Oberbach, A., et al., *Altered fiber distribution and fiber-specific glycolytic and oxidative enzyme activity in skeletal muscle of patients with type 2 diabetes.* Diabetes care, 2006. **29**(4): p. 895-900.

251. Guney, H., et al., *Is there any loss of ankle proprioception in diabetic patients without neuropathy?* Isokinetics and Exercise Science, 2013. **21**(4): p. 317-323.

252. Darlington, C.L., et al., *Comparison of visual–vestibular interaction in insulin-dependent and non-insulin-dependent diabetes mellitus.* Neuroreport, 2000. **11**(3): p. 487-490.
253. Stansberry, K.B., et al., *Impairment of peripheral blood flow responses in diabetes resembles an enhanced aging effect.* Diabetes care, 1997. **20**(11): p. 1711-1716.
254. Ebenholtz, S.M., *Motion sickness and oculomotor systems in virtual environments.* Presence: Teleoperators & Virtual Environments, 1992. **1**(3): p. 302-305.
255. Domeyer, J.E., N.D. Cassavaugh, and R.W. Backs, *The use of adaptation to reduce simulator sickness in driving assessment and research.* Accident Analysis & Prevention, 2013. **53**: p. 127-132.

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