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## Effects of acute alcohol intoxication on human sensory orientation and postural control

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# Effects of acute alcohol intoxication on human sensory orientation and postural control



**LUND**  
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*Fredrik Modig*

AKADEMISK AVHANDLING

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Title and subtitle Effects of acute alcohol intoxication on human sensory orientation and postural control	
Abstract <p>Alcohol affects balance and is related to falls and injuries. Even though alcohol effects on balance and eye movement have been studied before we know less about the dose and time dependent effects and how each supportive sense to balance contributes during acute alcohol intoxication.</p> <p>The purpose was to investigate parallel effects of acute alcohol intoxication on balance (postural control), balance efficiency (adaptation) and its supporting senses. We included 25 healthy subjects on three different test occasions during acute alcohol intoxication of 0.06% and 0.1% blood alcohol concentration (BAC) and sober, ensured using a real time breath analyzer.</p> <p>Balance was evaluated with a balance force plate and a 3D-system for individual body segment detection. Spatial orientation and eye movements were measured. Foot sensation was measured when sober and the subjective feeling of intoxication was continuously followed.</p> <p>Instability was considerably higher at 0.1% BAC compared to 0.06% BAC and was more obvious in the medio-lateral (side to side) direction compared to the anterior-posterior (front and back). When standing balance is perturbed by vibration of the calf muscles, body movement increases. Repetition of these perturbations drives balance learning (adaptation) in sober subjects and the result is a reduction of body movement. When intoxicated however, normal adaptation is reduced or abolished.</p> <p>Whilst visual feedback is important for maintaining stability, it didn't fully compensate for being intoxicated and contradictorily decreased medio-lateral stability. This could partly be explained by the impaired eye movements by intoxication. Additionally, being intoxicated increased visual dependence, i.e., the use of visual senses for positioning ourselves within the environment. Together, it illustrates that being intoxicated causes an over-reliance on visual senses which aren't always helpful.</p> <p>When visual senses are absent, intoxicated subjects will rely upon foot mechanoreceptive sensation for standing balance, and change their balancing strategy by pivoting more prominently forwards and backwards around the knee level. One's own perception of drunkenness matches slow eye movements as well as upper body movement.</p> <p>In summary, alcohol intoxication at levels common in society, has a widespread disturbing effect on the components of the human balance system, from each sensory system to the Central Nervous System's integrative and cognitive processing, and also effects adaptive ability, the summation of which produces a complex attack on postural and oculomotor behaviors.</p>	
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# Effects of acute alcohol intoxication on human sensory orientation and postural control



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*Fredrik Modig*

Doctoral Dissertation Series 2013:24

Oscar Wilde once wrote in the late 1900<sup>th</sup> century “I have made an important discovery...that alcohol, taken in sufficient quantities, produces all the effects of intoxication.”

I have taken more out of alcohol than alcohol has taken out of me. ~ Winston Churchill

In vino veritas ~ Gaius Plinius Secundus

Front cover illustrates an example of alcohol in the social life.

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# List of publications

This thesis is based on the following articles. Each study is represented by Roman numerals:

- I. Modig F, Patel M, Magnusson M, Fransson PA.  
Study I: Effects of 0.06% and 0.10% blood alcohol concentration on human postural control.  
Gait Posture. 2012 Mar; 35(3):410-8.
- II. Modig F, Patel M, Magnusson M, Fransson PA.  
Study II: Mechanoreceptive sensation is of increased importance for human postural control under alcohol intoxication.  
Gait Posture. 2012 Mar; 35(3):419-27.
- III. Hafström A, Modig F, Karlberg M, Fransson PA.  
Increased visual dependence and otolith dysfunction with alcohol intoxication. Neuroreport. 2007 Mar 5; 18(4):391-4. \*
- IV. Fransson PA, Modig F, Patel M, Gomez S, Magnusson M.  
Oculomotor deficits caused by 0.06% and 0.10% blood alcohol concentrations and relationship to subjective perception of drunkenness.  
Clinical Neurophysiology. 2010 Dec; 121(12):2134-42.
- V. Patel M, Modig F, Magnusson M, Fransson PA.  
Alcohol intoxication at 0.06 and 0.10% blood alcohol concentration changes segmental body movement coordination.  
Experimental Brain Research. 2010 Apr; 202(2):431-43.
- VI. Modig F, Fransson PA, Magnusson M, Patel M.  
Blood alcohol concentration at 0.06 and 0.10% causes a complex multifaceted deterioration of body movement control.  
Alcohol. 2012 Feb; 46(1):75-88.

\* Previously presented in the thesis “Visual influences on vestibular compensation and postural control” by Anna Hafström.

# Definitions & abbreviations

**Adaptation:** A change in structure, form or habit of an organism enabling it to function adequately in a new or changed environment.

**Afferent:** Ascending sensory information from our sensors to the CNS.

**Alertness:** The state of awareness to handle a sudden change in the environment.

**Angular position:** Position coordinate defined from using distances and angles relative to a reference point, e.g., describing body leaning in degrees relative to the ankle position.

**Attention:** The cognitive ability to concentrate on one aspect while simultaneously ignoring others.

**BAC:** Blood Alcohol Concentration.

**CNS:** Central Nervous System.

**Efferent:** Signals which descend from the CNS and cause movement.

**EMG:** Electromyography is a technique for recording the electrical activity produced by the muscles from which one can analyze details of human movement.

**ENG:** Electronystagmography is a method where the position and movements of the eyes can be determined by measuring the electric activity next to the eyes.

**Feedback mechanisms:** A homeostatic cycle where one key function (i.e., movement) needs to be kept tightly regulated. To do this a control system compares the actual and the desired states and generates actions to minimize the difference.

**Feedforward:** An anticipatory process which generates counteractive measures to an expected event.

**Internal model:** A neural representation in the CNS of the human body (body scheme). We hold a virtual picture of body position and what might happen to the body if an expected event occurs i.e., I slip to the right if I put my right foot on ice.

**Linear movement:** Movement in each orthogonal plane, e.g., in anteroposterior, lateral and vertical direction.

**Mellanby effect:** Causes the same BAC level to have more severe detrimental effects on CNS functions when the BAC level is in increasing state than in decreasing state.

**Metabolization:** The chemical process where some substances are broken down to generate energy for vital body processes while other substances are synthesized.

**Postural control:** The sensorimotor process ensuring that stability is maintained under upright stance and body movements.

**Perturbation:** A disturbance affecting the body stability.

**Proprioception:** Senses the positions and movements of body segments relative to each other and to the ground from sources like muscles, tendons, joint and pressure sensors.

**Re-weighting:** Shifting the contributions from the (movement) sensors.

**Torque:** Energy used to produce a rotation movement around an axis, e.g., the ankle joint.

**Torque variance:** Describes the distribution size of the energy used towards the surface to maintain stability.

## Thesis at a glance

Study	Question	Methods
The assessments in all studies I-VI below were performed at		
<b>I</b>	What are the effects on postural control (balance) and adaptation (enhancements from learning) of acute alcohol intoxication?	Posturography with recordings of body sway in quiet stance and balance perturbations by means of vibration to calf muscles, when subjects were standing with eyes closed and open.
<b>II</b>	What role does mechanoreceptive sensation have for maintaining balance and adaptation during acute alcohol intoxication?	Mechanoreceptive sensation was measured when non-intoxicated. Posturography data from quiet stance and with perturbations with eyes closed and open was correlated to mechanoreceptive data.
<b>III</b>	How is the spatial orientation influenced by acute alcohol intoxication?	Visual spatial orientation tests were performed with and without distorting visual illusions.
<b>IV</b>	How does acute alcohol intoxication affect eye movements?	Smooth pursuit eye movements and saccades were recorded with ENG. Self-perception of drunkenness was correlated to eye movement properties.
<b>V</b>	How is the movement pattern of the head, shoulder, hip, knee and ankle affected by acute alcohol intoxication?	The position of the individual body segments was measured with a 3D motions detection system. Self-perception of drunkenness was correlated to body movement pattern.
<b>VI</b>	How is the size of the body movements affected during acute alcohol intoxication?	Position of the individual body segments was measured with a 3D motions detection system.

Results	Conclusions
0%, 0.06% and 0.1% BAC (Blood Alcohol Concentration).	
<p>The stability declined non-linearly with increasing BAC. Alcohol decreased the stability proportionally the most in lateral direction and decreased the normal stability adaptation over time. Vision increased stability mostly in anteroposterior direction, though not as effectively as when sober.</p>	<p>Alcohol decrease postural control and adaptation. The size of this decline is dose, time and direction specific. Vision enhances balance during intoxication as well, but to a lesser degree as when sober.</p>
<p>Lower values of vibration perception (better vibration sensation) correlated well with better balance during 0.1% BAC alcohol intoxication during perturbations with eyes closed. With increasing BAC there was a stronger relationship between good stability and good mechanoreceptive sensation.</p>	<p>Good mechanoreceptive sensation is especially important when intoxicated. Postural control relies gradually more on mechanoreceptive sensation during higher BAC intoxication.</p>
<p>Alcohol caused a decrease in sensing the spatial orientation correct. Moreover, while intoxicated the orientation became more easily distracted by visual illusions.</p>	<p>When visual and vestibular-proprioceptive information are contradictory, alcohol intoxication seems to cause a reweighting to rely more on vision.</p>
<p>Smooth pursuit velocity accuracy, smooth pursuit gain and saccadic velocities started to be decreased at 0.06% BAC. Saccade latency and saccade accuracy were affected at 0.10% BAC. The ratio between saccade velocity and saccade amplitude decreased with increased alcohol intoxication. Self-perceptions of drunkenness correlated well with changes in smooth pursuit velocity accuracy.</p>	<p>Some smooth pursuit and saccade function characteristics were more sensitive to alcohol than others. Several eye movement properties declined or were deformed dose-dependently by alcohol. Worse smooth pursuit velocity accuracy was strongly correlated to feeling more drunks.</p>
<p>The body movement pattern gradually changed over time at 0.10% BAC during balance perturbations with eyes closed, from first using mostly the ankle joint as means to control stability to also using the knees during the latter part of the stability tests. More concurrent movements of the upper body correlated with feeling less drunkenness.</p>	<p>During perturbations with eyes closed, movements at the knees increasingly used for stability regulation to maintain stability. A changed upper body movement pattern may be important for the self-perceptions of drunkenness.</p>
<p>All body movements increased significantly by increasing BAC. The knee movement amplitude decreased noticeably with eyes closed during the latter part of the stability tests in anteroposterior direction at 0.1% BAC. Sensorimotor adaptation deteriorated with increasing BAC. There was a non-linear increase, especially in lateral direction, of the body movements over time. Vision decreased the body movements but provided a weaker contribution to postural control during intoxication.</p>	<p>The effects of alcohol were larger with increasing alcohol intoxication and during the latter periods of the stability tests. Alcohol affects adaptation to the worse. The knee movement had a changed roll in the end of the balance test with eyes closed, which suggests that a more complex multi-segmented movement pattern had to be used to cope with the effects of alcohol.</p>



# Introduction

Almost 6 million years have passed since the first putative hominids, the *Orrorin tugenensis*, effectively started to use their senses to ensure a stable upright stance (1). The upright human uses the combined information from the vestibular system, vision and somatosensory systems to maintain balance while standing, walking and running. However, the information from these senses can be distorted by different factors such as by drinking alcohol. Alcohol has presumably been consumed by humans since late stone age since about 10 000 BC (Neolithic period). Archaeological findings of beer jugs from that age suggest that alcohol was already during this early period an intentionally fermented beverage (2). Alcohol has had an intricate role in society throughout the history, serving an important role in social events as well as in religious ceremonies but also served a role for trading and as payment. Early in history, various drinking beverages were developed such as wine, spirit and beer, each kind designed to use available regional resources and to be in line with local cultural traditions. Hence, the alcoholic beverage is strongly associated with human culture and lifestyle, a situation not likely to change soon.

Alcohol generally represents a drug that people uses for pleasure drinking but it also has a number of side effects. Alcohol affects a number of human functions and organs. Extensive long-term use harms the body organs, commonly showed by cirrhosis of the liver and atrophy of the cerebellum. Fall-related injuries, such as traumatic brain injury and fractures requiring hospitalization, are often caused by alcohol (3). Additionally, Johnson et al has also showed that the severity of the injury received from alcohol-related falls is associated with the level of blood alcohol concentration (BAC) (4). This finding suggests that alcohol may have a more intricate influence on postural control than merely causing a decrease in balance and orientation.

Although the effects of alcohol on balance have been studied before, only recently have a new generation of equipment allowed exact assessment of BAC in real-time and, thus, allowed accurate studies of the dose dependent and time-varying effects of alcohol intoxication. Hence, many of the published studies about alcohol, postural control and oculomotor functions are outdated. The objective of this thesis is to address this problem and further investigate the effect of alcohol intoxication on the different sensory systems and balance control functions. Hence, to better elucidate the effect of this commonly used social drug, it is of major importance to determine the relationship between alcohol levels and the functional performance.



# Alcohol

## **Alcohol**

Acute alcohol intoxication is well recognized by slurring of speech, unstable gait (walking) and posture (standing), confusion, elation, increased self-confidence, inaccurate movements etc. At extreme intoxication levels, characteristics include euphoria, changes in emotion; aggression and submission, vertigo and even multiple system failure resulting in death.

## **Alcohol – Ingestion, uptake and metabolism**

Alcohol, also termed ethanol ( $C_2H_5OH$ ) is highly lipid-soluble and is rapidly absorbed through the mucous membranes in the esophagus, stomach and intestines. Absorption is by pure diffusion. After absorption, the alcohol enters the blood stream and is quickly distributed throughout the total mass of water in the body. The distribution volume i.e. the actual average total body water in males is 65% of the total body weight and 54% of the total body weight in females. The alcohol blood uptake is highly dependent on the speed of which alcohol is emptied from the stomach. This is because of the faster intestinal absorption. Stomach contents delay absorption and an empty abdomen therefore makes the absorption faster. After intestinal absorption, alcohol enters the portal venous circulation passing on to the liver. If the uptake is rapid, the alcohol degrading systems in the liver (first hepatic metabolism) become saturated. More alcohol then escapes this first metabolism passage without being metabolized, increasing its potency. Maximum BAC is reached approximately 15 minutes to 2 hours after intake.

When alcohol has entered the systemic circulation it will be consecutively metabolized by the liver. About 90% of total alcohol elimination will be metabolized by the liver. Alcohol metabolism has almost linear kinetics, except when the concentration is very low. The properties of alcohol metabolism rate have been under debate and some investigators have suggested that the degrading slope is steeper with increasing intoxication levels (5). In general, an adult metabolize 0.08 – 0.20 g alcohol / kilogram / hour. In a fully grown man (70kg) that equals a total of 7 g/hour (6, 7). Furthermore, 5-10 % of the alcohol not degraded by the liver is metabolized by other organs and some is also excreted in sweat, urine and the air. The ratio of alcohol concentration in blood and alveolar air, measured at the end of deep breath expiration, is relatively well correlated (8). This is the basis for breath tests.

Body weight may influence the alcohol concentration degradation slope. This is discussed by Jones et al. claiming that individuals with higher body mass index (BMI) have a steeper slope which means that heavier people may degrade alcohol faster (5). People with higher BMI also reach higher BAC after the same intake of alcohol per kilogram than humans with normal body fat distribution. One report

states that people with relatively small volume of distribution of alcohol, i.e. proportion of body water, degrade alcohol faster. This could explain why women metabolize alcohol faster than men and that elderly degrade alcohol faster than the young (9).

### **Alcohol – Effects on cellular level**

The presumed alcohol effects on cellular level are considered to be:

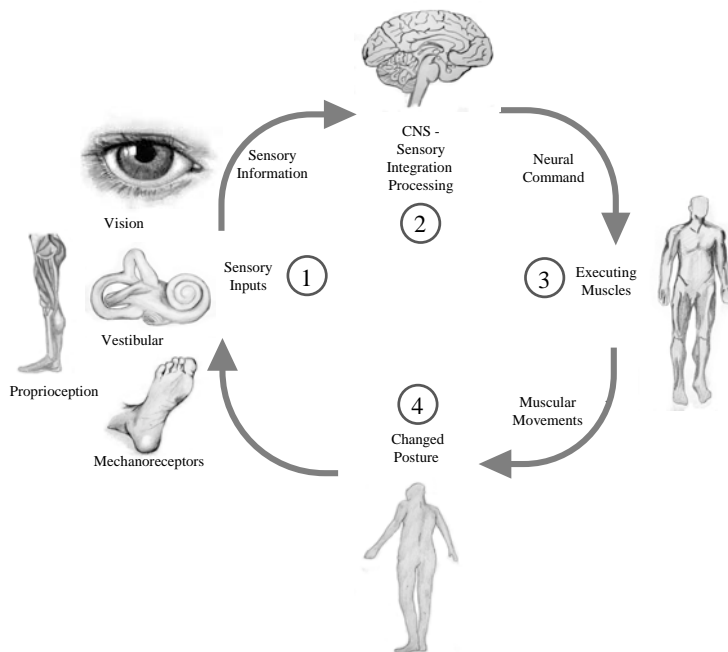
- Enhancement of GABA-mediated inhibition.
- Inhibition of calcium entry through voltage-gated calcium channels.
- Inhibition of NMDA receptor function.
- Enhancement of excitatory effects produced by activation of nicotinic acetylcholine receptors and 5-HT<sub>3</sub>-receptors.
- Inhibiting the flow of sodium ions across the cell membrane

These mechanisms explain why acute alcohol intoxication diminishes the flow of nerve action potentials and causes difficulty of nerve firing (10-14). Increasing BAC causes further deterioration of nerve impulse transmission. The presence of alcohol in the CNS can interfere with the transmission of nerve impulses at the synapse (13, 14). The effects could be both inhibitory and excitatory dependable on which type of neuron is affected. The inhibitory neurons are often affected first (15). Electrophysiological studies have demonstrated direct inhibition by alcohol of L-type voltage gated calcium channels at nerve terminals (13, 14). The L-type voltage gated calcium channels spread throughout the pre-synaptic membrane and motor end plates, including the vestibular nucleus complex. Substantial inhibition of voltage-gated calcium channels by alcohol, which increases non-linearly with increasing alcohol intoxication (16), may lengthen the conduction time at synapses and neuromuscular junctions, leading to increased latency of motor function responses (13, 14). An intoxicating amount of alcohol could significantly reduce the amplitude of mono- and poly-synaptic reflexes (17), and prolongs the latency and reduces the amplitude of long latency muscle responses (18). Furthermore, vestibular nucleus neurons are more sensitive to alcohol than neurons in the trigeminal and medial geniculate nuclei (19).

The effect of alcohol is individual and depends on personal sensitivity for alcohol and blood plasma alcohol concentrations. The rising alcohol concentration produces greater effects on the body functions than a falling concentration or at steady state, even if the measured blood alcohol concentration is identical. This is called the Mellanby effect (11, 20, 21). This phenomenon is seen almost from the beginning of drinking until after approximately 90-120 minutes (7).

# Postural control

The human body is not biomechanically stable in upright stance but requires a control system that continuously makes small corrective movements. This control system, that is noticeable in posturography recordings as a small but continuous sway, is commonly called postural control or balance. Postural control is based on continuous integration of sensory information from three dominant sources: visual, vestibular (inner ear) and somatosensory receptors (proprioceptors and mechanoreceptors) (22). The Central Nervous System (CNS) gathers and processes this sensory information to assess the position and motion of the body (23). The CNS will interpret, evaluate and process the information through integrative centers such as the cerebellum (24). Timmann et al have shown that cerebellar lesions effect the scaling of the size of the postural response (25). The CNS then generates and coordinates multiple motor outputs to muscles throughout the body (26). Johansson et al has described postural control as a constantly ongoing process which cycles through corrective feedforward (predictive) and feedback (reactive) regulative movement control systems, see figure 1 (27).



**Figure 1:** Schematic illustration of human postural control and orientation. The functions denoted by numbers in the figure are described in the sections below.

Muscles, responsible for expressing CNS commands enable the body to take the appropriate stance for any given situation. Some muscular movements are of conscious nature but in normal every day behavior postural control is a self-regulating, automatic process which can be looked upon as an amalgamation of automatic reflexes. Some of the most important reflexes are:

**Stretch reflexes** are initiated by an initial muscle stretch, which generates nerve signals from muscles spindles in the muscle. The CNS takes care of the afferent input and sends signals to the muscles of the opposite side of the body than the stretched muscle to contract. This is an important reflex especially for handling rapid externally produced balance perturbations that is threatening balance.

**Vestibulo-ocular reflexes** are important for eye movements. The vestibular system detects movement of the head and sends signals to the vestibular nuclei. This initiates response to the eye muscles to relax or contract so the eye movements can move in the opposite direction to the head movement. The reflex helps to stabilize a clear picture on the retina when the head is moving (28, 29).

**Vestibulo-colic reflexes** regulate head and neck position and movements. Neck muscles contracts or relaxes to restrain gravity and to keep the head upright on the shoulders. Subsequently there is a reflexive change of the body position which is relative to the head. This reflex assures that the body can consider the vestibular and visual information obtained from receptors located in the head, for its stability regulation (28, 29).

**Vestibulo-spinal reflexes** regulate location and motion of the trunk and limbs. When groups of muscles contract, on one side of the body, other similar muscles groups relax on the opposite side. When unexpected head movements or unexpected body movements activate this reflex, then the reflex quickly initiate appropriate actions to support maintaining upright stance and prevent falling (28, 29).

**Reticulo-spinal reflexes** are important for preservation of balance and consist of a tract between the reticular formation and the spinal motor neurons.

The simple act of standing is a common task though it depends upon complex actions.

Humans have an intricate physique, with many biomechanical degrees of freedom allowing for various movements (30). The balance control is still highly effective and very precise even though it is automatic and normally managed without conscious control. When standing unperturbed or perturbed, an almost standardized movement pattern of the body segments is used for maintaining postural stability. This movement pattern is usually called ankle strategy or single link pattern (31). One characteristic of this movement pattern is that the movements of all body segments are concurrent with the ankle joint acting as the

only movement joint. The stabilizing muscular corrective movements are mainly expressed by adjusting the ankle joint angle relative to the other body segments. During more demanding situations, this simplified movement strategy may become insufficient and is consequently replaced by strategies where corrective movements are introduced using other joints such as at the hip or knee. Such multi-segmented movement patterns may be more appropriate for the situation (32).

### **Postural control – Alcohol effects**

Posturography (recording body movements and actuated forces to the ground with a force platform) has been used in several previous studies on alcohol intoxication and balance (12, 33-35). In earlier studies of postural control sway area and sway amplitude were enlarged by alcohol intoxication with eyes open and eyes closed (34, 36-38). Studies have reported that BAC above 0.07-0.08% impairs postural control in unperturbed standing (34, 39, 40). Alcohol intoxication leads to detrimental effects on both the sensory and motor systems (41) and is likely to have profound effects on body movement and its control while standing, previously depicted by others including Ledin and Belmeguenai (10, 42).

### *The sensory inputs*

The sections below focus on the sensory systems; each of which provide supportive information to how we can move, stand, touch objects and interact with the environment i.e., reading a book (1 - See Figure 1). These sections also describe how alcohol intoxication can impair the information from each of these sensory systems.

#### **Vision**

Vision provides information about the orientation of objects in a person's surroundings (e.g. seeing the horizon) as well as movements in the visual surround (43). It provides the CNS with information that allows us to interact with a highly dynamic environment. Vision gives us feedback data, a reference frame, of our own posture and movement and how it compares to the surroundings. It also supports feedforward motor control which helps us to anticipate the continuous change of the surroundings we interact with. Vision is of importance but not essential in regulating standing postural control (44).

Eye movement maintains the position of an object of interest upon the fovea during self or object motion. The retina then forms visual information which is subsequently interpreted by the CNS. Eye movements may be divided into different types as voluntary and reflexive (43). Among the reflexive eye movements, there are convergence, the vestibule-ocular and the optokinetic reflexes. Among voluntary eye movements there are smooth pursuit and voluntary saccades, some authors also consider cancellation of the vestibule-ocular reflex as

a voluntary eye movement (43). Smooth pursuit eye movements are used to follow moving objects and to keep the image of the object stable on the fovea. Voluntary saccades are high-velocity ballistic eye movements used for fast redirections of gaze, for example between different fixations points and to bring an object of interest onto the fovea (43).

Smooth pursuit eye movements are governed by several brain areas in the parietal and occipital lobe, close to the visual cortex. Voluntary saccades are initiated from the contra lateral side of the frontal lobe in the supra nuclear gaze direction center. Thus, the gaze direction to the right side is directed from the left frontal lobe and vice versa. Both smooth eye pursuit and saccadic path systems converge towards the pontine gaze center (PBC) in mesencephalon. PBC guide eye movements via the Abducens and the Oculomotor nuclei. These sites send signals to the eye movement muscles. PBC is also in direct connection to the contralateral Vestibular nucleus. This pathway guides the vestibular-ocular reflex, VOR.

Nystagmus is the clinical term for eye movements (slow deviation followed by a fast returning movement (beats)) which occurs when we are being rotated or tilted. However, if these occur when we are stationary, we experience rotational sensation (vertigo). These nystagmic eye movements are classical signs during acute vestibular disease (i.e., neuritis, labyrinthitis, meniere's disease). Nystagmus can help to confirm vestibular disorders.

### **Vision - Alcohol effects**

Smooth pursuit and saccadic eye movements have been studied frequently during alcohol intoxication. These studies suggest that alcohol intoxication generally decreases the accuracy of our eye movements when tracking a moving target (45-49). Alcohol intoxication can also slow down the speed of the eye movement made and delay the responses making it take longer time for the eyes to start moving, i.e., increase latency (13, 14). It's also well-known that alcohol can cause blurring or double vision (oscillopsia), though these manifestations are likely to be from impaired vestibular signals.

Alcohol Induced Gaze Nystagmus (AGN) appears at and above approximately 0.08 % (50, 51). This nystagmus always beats with the fast phase in the direction of the gaze and is uninfluenced by the position of the head.

### **The Vestibular System**

The vestibular system consists of the otoliths and the labyrinths and is positioned in the inner ear. The labyrinth includes the anterior, posterior and lateral semicircular canals, which detect the head's acceleration in space in the respective canals' sensitive direction during rotational head motion. The otoliths consist of the utricular and saccular macula organs, which continuously sense linear acceleration, e.g., gravitational force and linear accelerations or decelerations

affecting the head (52). The gravitational information provides an orientation frame of reference in space on the basis that the direction of the gravitational forces always is constant. Afferent information from the vestibular system to the CNS is important for maintaining balance. The vestibular system produces the VOR, which is an important reflex that ensures that angular head accelerations or tilt make the eyes move reflexively with an identical acceleration but opposite direction to the head acceleration.

### **The Vestibular System - Alcohol effects**

Alcohol intoxication affects vestibular function (53). It has a direct effect on the cupula of the semicircular canals which sends signals to the CNS about angular head accelerations or decelerations (37). Neurophysiologically, this is reflected by the positional alcohol nystagmus (PAN). Aschan and Bergstedt showed that positional alcohol nystagmus (PAN) were induced at 0.08% BAC, but later studies shows that it may appear at lower BAC levels as well, for example, it could start as low as 0.025-0.040% at BAC (54). The reason for PAN is that alcohol has lower density than the endolymphatic fluid in the semicircular canals. PAN occurs when the alcohol concentration is different in the cupula and in the endolymphic fluid. Changes in alcohol concentration tend to affect the cupula first due to its close proximity to blood vessels. Thus, before the alcohol has reached the endolymphic fluid the cupula will be lighter than the endolymphic fluid.

To our knowledge, there are only two studies about how alcohol affects the otolith information from using the SVV and SVH test. Both suggest that alcohol probably has no effect on the otolith information (50, 55).

### **Proprioception**

Proprioceptors provide information about the orientation of the body during static postures and movement (e.g. knowing if you are standing upright, leaning or moving the feet). They are found in joints, joint capsule, ligaments, tendons and muscles and consist of joint receptors, Golgi tendon organs (GTOs) and muscle spindles. The majority of the proprioceptors are able to perceive changes up to a frequency of 200 Hz. It has been proposed that proprioception is the most important sensory system for postural control, responsible for maintaining balance and for setting off automatic balance responses during perturbations, for example to unexpected horizontal surface displacement (56, 57). Receptors in joints are anatomically located around the connective tissue. They react on physical stimuli such as movement or mechanical pressure induced by movement. GTOs are located inside tendons and are responsive to stretch of the tendon. GTOs are sensitive to large changes in tendon length and are mainly concerned with signaling to the CNS how hard the muscle is contracting. Muscle spindles are located within skeletal muscles and their concentration is more numerous in muscles requiring accurate movements, such as deep cervical muscles or the finger

muscles. They constantly sense muscle length and transmit it through the nerve impulse frequency which correlates to the muscle length. This characteristic admits the muscle spindles to dynamically transmit any contraction or stretch of the muscle and its velocity.

### **Proprioception - Alcohol effects**

The findings made by Wang et al. suggest that proprioception is affected by alcohol intoxication. Wang performed proprioceptive arm movement tests to evaluate the Mellanby effect. These tests showed that the arm proprioception was significantly deteriorated during repeated tasks when comparing sober with alcohol intoxicated at 0.05-0.075 BAC (21).

### **Mechanoreceptors**

The soles of feet supply the CNS with somatosensory information from cutaneous, low-threshold, mechanoreceptors on the plantar soles (58). This afferent data is particularly important when balance is perturbed (59). These mechanoreceptors provide detailed temporal and spatial information about the contact pressures on the soles (60). This is especially important for sensing changes in body orientation (61).

Mechanoreceptors are divided into slowly adapting (Ruffini corpuscles and Merkel disk receptors) and rapidly adapting (Pacinian and Meissner's corpuscles) (56, 62). Slowly adapting mechanoreceptors signal constantly and accurately how the pressures are spatially and sequentially distributed on the skin to the CNS (63) i.e. the foot sole-surface interaction. Rapidly adapting mechanoreceptors signal the amplitude and the rate changes of the pressure applied on the skin to the CNS (63) i.e. the changes of posture necessary for postural stability (64).

### **Mechanoreceptors - Alcohol effects**

To our knowledge, there are no studies performed on acute alcohol effects on mechanoreceptive sensation, which is our ability to feel touch, pressure or vibration.

Also chronic alcoholics can suffer from permanent damage of the peripheral nerves i.e. polyneuropathy, which may delay processing on mechanoreceptive signals (65, 66).

## *CNS – Integration and processing of sensory input*

Kinesthesia is the common name used to describe the internal body model representing the persons own body position and movement (2- See Figure 1). This body model is built up by information from the different receptor systems and involves several areas of the brain which are crucial for motor reflexes. The integration process needs continuous attention (67-69) particularly when information from the receptor systems are incomplete, distorted or absent (70, 71).



However, the system for maintaining the standing posture may still work satisfactory because of functionally overlapping sensory systems (72) which allows the CNS to use the information from the receptor systems providing the most accurate information and subsequently to disregard from receptor systems that appears to be distorted or are missing. This ability of CNS to select and rate the importance of information from various receptor systems to find and use the most accurate information is called re-weighting. The overlapping effects are not just functional but also physiologic and anatomic (73). The integration process is localized in the cerebral cortex, thalamus, brainstem, vestibular nuclei, cerebellum and spinal cord. Cerebellum is also an important center for sensory integration and for the internal representation of body mechanics (74-77). Afferent data reach the CNS at various levels (78, 79). The feedforward system mainly consists of the cerebral cortex, basal ganglia, brainstem and the cerebellum (78).

### **CNS - Alcohol effects**

The alcohol effects on the CNS are both widespread and complex. Alcohol intoxication can significantly delay corrective balance responses (18, 34) and possibly synaptic plasticity and learning, possibly through impairments of cerebellar function (42). Acute alcohol intoxication is also accompanied by otoneurological signs of spinocerebellar and vestibulocerebellar ataxia (80). Since alcohol intoxication causes disrupted visuo-vestibular functions, sensory information from visual and vestibular receptors might not be deemed accurate by the CNS. Some of these effects could be explained by that the presence of ethyl alcohol in the CNS and its effects on cellular level. Thus, alcohol leads to detrimental effects on both the sensory and motor systems which are important for a fully functioning CNS (41). We have found no published studies on acute alcohol intoxication on sensory re-weighting.

### **Postural control and Adaptation**

Postural control adaptation is a learning mechanism which enables a person to improve their balance control over time and after repeated challenges (81). It makes the balance control more efficient and the movement pattern adopts a more economic configuration. Adaptation in standing minimizes costs including energy demands, forces, fatigue, inaccuracy, jerkiness etc. When healthy sober subjects are exposed to repeated balance challenges the postural control system usually introduces an adaptive process allowing them to manage the balance challenges more easily after a learning phase (82). Sensory re-weighting may be a part of the adaptation process and altered feedback and feedforward motor control responses (83) resulting in a decreased fall risk (31, 84, 85). Human postural control adaptation also involves recalibration of motor programs, sensorimotor pathways, and strategies, such as changes of the body movement pattern (31, 85). Hence, healthy individuals should be able to learn the characteristics of the destabilizing effects when repeatedly exposed to the same kind of balance perturbations, and set

their balance system to minimize these effects (86, 87). Cerebellar impairments often influence the adaptation to postural challenges (83, 88).

### **Postural control and adaptation - Alcohol effects**

The maintenance of balance under sensory irregularities and hence adaptation to repeated balance perturbations demands attention (67, 89). The impairing effects of alcohol on attention are well-documented (90). Acute alcohol intoxication decreases attention (91) and studies have shown that alcohol disrupts performance on divided attention tasks that involve simultaneously allocating attention to two or more activities. Alcohol also disrupts tasks requiring alertness and tasks that requiring prolonged attention to changing stimuli (92-94).

### *Executing muscles*

When the afferent information is received, interpreted and processed, the CNS has to generate a postural response. This response is effectuated through issuing neural commands to muscles (3 - See Figure 1). The basal ganglia are of central importance in planning, control and initiation of motor programs (95). Cerebellum is essential for controlling the timing and size of the muscle activity (95) but also for controlling the coordination of the balance responses (96). The primary motor cortex initiates the muscular responses and these are executed by the brainstem and spinal cord (97).

### *Changed posture – Biomechanical constraints and imbalance*

The biomechanical design of the upright standing human body is commonly simplified to be seen as an inverted pendulum where the feet are fixed to the ground, and the ankle serves as the pivotal point of movement; the other body segments are free to move but do so in unison (4- See Figure 1). However, this simplified model is not always sufficiently representative in describing other postures, when other joints take on the lead role. In an anterior-posterior direction, the different segments located on either side of a joint can move independently though movement of one segment has a direct effect on another (98). Movement of one segment therefore causes a total change of posture (99). The segmental specific function also depends on the flexibility in the joints, muscles and tendons (27).



# Aims of the thesis

The general aim of the thesis was to explore how alcohol intoxication levels, commonly encountered among non-abusers in every day society, affect the balance system in healthy human beings.

The main aims in each study, of which this thesis is based on, are listed below:

- To assess alcohol effects on human postural control at socially commonly encountered levels of alcohol intoxication. (Paper I).
- To examine the role of mechanoreceptive sensation in human postural control during alcohol intoxication (Paper II).
- To examine how the spatial orientation using visual frame of references is affected by alcohol intoxication (Paper III).
- To determine to what extent oculomotor function is affected by alcohol and if it is correlated to the subjective perception of drunkenness (Paper IV).
- To investigate if and how the segmental body movement pattern is affected by alcohol (Paper V).
- To investigate if and how the size of the body movements are influenced by alcohol (Paper VI).



# Material and methods

## The study design

Our objective with these studies was to investigate the effects of alcohol on postural control, oculomotor functions and their coexisting different sensors. We constructed a solid test setup for evaluating each sense during alcohol intoxication at pre-specified levels of 0.0%, 0.06% and 0.1% blood alcohol concentration (BAC). The BAC was frequently monitored with a reliable and accurate breath analyzer. To minimize confounding factors all tests were made on the same 25 healthy test participants in similar test conditions. Alcohol dosing, intake and metabolism were thoroughly studied to give BAC levels as close as possible to target level.

During the studies at pre-specified BACs we considered methodological problems such as, weight standardized alcohol dosages, anthropometrical variability, gender and physiological variations in the absorption rate of alcohol. This could result in inter-subject BAC differences, both in peak BAC and duration of each of the three phases (ascending, plateau and descending) of BAC level (5, 9). These influencing factors are exemplified in the study on human postural control and alcohol intoxication by Nieschalk et al. (34) showing that the BAC in the 30 subjects assessed ranged from 0.022% to 1.59%, 30 min after consumption. Before the main studies took place, a pilot study involving 4 persons was carried out to evaluate the accuracy of the test procedure. All subjects were investigated at similar BAC levels and in the same alcohol metabolism phase, meaning that systematic biases from the Mellanby effect were eliminated. Moreover, systematic findings made in a large group of subjects assessed at the same BAC means that the statistical evaluation power becomes more accurate, and specifically, it ensures that responses recorded at the investigated BAC level are more likely to be representative of a larger population.

## Subjects

Twenty-seven consenting healthy adults initially volunteered to participate in the study. Two participants from this group were excluded: one for not reaching intended BAC and one due to pathological SVH-V test when sober. The final study group consisted of 25 participants (except in study III), 13 women and 12

men of mean age 25.1 years (range 19-41), mean height 1.75 m (range 1.60-1.92), mean mass 68.8 kg (range 50.05-106.3) and mean Body Mass Index 22.2 (range 17.9-30.7). Study III had 24 participants because of lack of data from one person. The subjects were paid to participate. Full informed written consent was obtained from the subjects before testing. The study was approved by the local ethics committee at Lund University, Lund, Sweden and performed in accordance with latest version of the Declaration of Helsinki.

The participants were screened for any medical reasons that might exclude them from participating in the study such as a history of vertigo, balance problems, inner ear disease, acute bacterial meningitis, major CNS trauma, cardiovascular disease or serious injuries involving their lower extremities or known eye movement disorders. The medical examination was supervised and performed by an Otorhinolaryngology physician and included hearing, visual and vestibular tests: the Weber test, otolith rod and frame test, eye movement saccade and pursuit tests, head impulse test and a headshake test using magnifying video glasses. All participants were accustomed to social drinking, but none of them reported any indications of alcohol dependency according to the Alcohol Use Disorders Identification Test questionnaire (AUDIT) developed by the WHO (100). AUDIT cut-off limit was set at a total score of 15, at the limit to possible harmful drinking. None of the participants were regular smokers. Participants were instructed not to consume any alcohol, sleep-inducing or revitalizing products, such as caffeine, 24 h before and during testing other than the alcohol provided to the participants. At the time of the study, no participant was on any form of medication (except contraceptive pills) and smoking was not allowed.

## Dosing, masking and measuring blood alcohol concentration

Each participant performed the tests at three different blood alcohol concentrations (BAC), at 0.0% (control), 0.06% and 0.10% in a randomized order using a Latin Square design. The tests were conducted once a week for three consecutive weeks and participants were blinded to the amount of alcohol they consumed. The tests were performed between 11.00 and 16.00 by all subjects to avoid possible circadian rhythm effects (101). The participants were instructed to only eat a simple breakfast or a light lunch 2 hours before the tests. After the meal they were told not to eat solids but their intake of caffeine-free fluids was not restricted. The subjects had 30 min in a quiet environment to drink 750 ml of either a mixture of 70% colorless ethanol and elderflower juice or only elderflower juice (0% BAC). Of note, elderflower juice was used because it masks the taste and scent of alcohol

particularly well. No concoction was distinctive, which decreases the chance of predicting the level of alcohol consumed. The amount of alcohol provided to each participant was depending on sex and weight, calculated to achieve the intended BAC. For women to reach 0.06% BAC they were given 0.6 g alcohol/kg body weight and men 0.7 g alcohol/kg. For women to reach 0.1% BAC they were given 1.0 g alcohol/kg body weight and men 1.1 g alcohol/kg. Thus, the alcohol amount given to the subject depended on the gender, weight and on the intended level of BAC level. Following formula was used to calculate individual alcohol amount for each test:

**Amount of liquid (Milliliters of 70% alcohol concentration) = body mass (kilograms) x amount ethanol (gram) (100%) per kilogram body mass / 0.7 (70% alcohol concentration) x 0.789 (conversion rate weight percent to volume percent)**

Calculating example of how much 40% Vodka women and men had to drink to reach to intended BAC level:

- Woman (60 kg) had to drink 11 cl (2,75 “standard drinks”) to reach about 0.06% BAC.
- Woman (60 kg) had to drink 19 cl (4,75 “standard drinks”) to reach about 0.1% BAC.
- Man (80 kg) had to drink 18 cl (4,5 “standard drinks”) to reach about 0.06% BAC.
- Man (80 kg) had to drink 28 cl (7 “standard drinks”) to reach about 0.1% BAC.

### **Measuring alcohol**

In recent years, the techniques to measure BAC in real-time through analysis of exhaled breath have vastly improved and modern devices now provide values highly correlated with blood analysis data (16). This means that the effects of alcohol intoxication at individual BAC levels can now be assessed much more accurately by using modern breath analyzers to monitor in real-time any change in BAC.

### **The Breath Analyzer**

The breath analyzer used in all studies I-VI was the Evidenzer (Figure 2) from Nanopuls AB in Uppsala in Sweden. It measures and analyzes, in real-time, breath alcohol concentration in end-expired breath with a precision of 0.001% (102). It corresponds to a relative precision or coefficient of variation of 4.7%, correlating very closely to BAC determined by venous-blood sampling and gas chromatography ( $r = 0.95$ ) (102). The Evidenzer™ system fulfills the requirements found in OIML R126E (1998) and has been approved by US department of transport.





**Figure 2:** Subject tested with the Evidenzer breath analyzer.

## Test procedure

After consuming the 750 ml drink in 30 minutes, alcohol concentration was measured every 15 min with a breath analyzer. Every 15 minutes the subjects were also instructed to provide a score of drunkenness using a visuo-analogue subjective drunkenness scale [VAS (0–100 mm)] at 0.00% BAC, 0.06% BAC and 0.10% BAC before testing. Subjects analogue scores were converted into numbers ranging from 1 to 10, where 1 = 0 mm= “sober” and 10 = 100 mm = “extremely drunk”.

The following criteria ensured that all participants were assessed during similar alcohol intoxication conditions:

- A plateau phase was identified in the BAC recordings with no further tendency of increasing BAC values.
- At least one BAC value was recorded with decreasing BAC level compared with peak BAC.
- The measurements were performed as closely as possible to planned BAC (0.06 or 0.10% BAC) in the descending BAC phase. The 0.00% BAC assessments were performed after about the same time as it took for the subjects to reach planned BAC in the alcohol intoxication tests. This procedure was used to avoid participants predicting their alcohol dose from when the assessments were performed after drinking the liquid.

When the subjects reached the intended BAC they were randomized to either perform the eye movement and rod & frame test series or the posturography test series first. When either test series was done, the BAC and VAS was measured again, and the subject thereafter performed the other test series.

## Assessing balance and sensory systems

### **Posturography - Assessing Balance using a Force Platform (Study I, II)**

One way to monitor the prospective risk of falling is to measure the individual's ability to maintain a stable upright standing position, particularly when the task is challenged (103). When we use a force platform to assess stable stance we name it posturography (Figure 3). A custom-made force platform recorded torques and shear forces with six degrees of freedom using force transducers with an accuracy of 0.5 N. Each subject stood barefoot on the force platform in a relaxed posture with arms folded across the chest. This posture was used to maintain consistency and to avoid inappropriate arm movements. The participant's heels were 3 cm apart and feet positioned at an angle of 30 degrees along guidelines on the platform.

To evaluate the capacity of the CNS to re-weight sensory information and the integrity of the sensory systems, experimental balance perturbations can be used to target one or more of the sensory receptors simultaneously. This approach can be used to distinguish between healthy subjects and patients with balance disorders (27). One way commonly used to perturb balance is by vibration of tendons and skeletal muscles, such as the calf muscles (Figure 3) (104, 105). This simultaneously increases the nerve signals from the muscle spindles and produces a proprioceptive illusion that the vibrated muscle is being stretched. The reactions thereafter are working to return the vibrated muscle to its supposed original length

(106). Calf vibration mainly induces body movement in the anterior-posterior direction (107, 108), but increases also the movements in lateral direction (89).

The balance challenging perturbations in these studies were induced by applying vibrations on the gastrocnemius muscles. The vibrations were produced by a revolving DC-motor (Escap, Geneva, Switzerland) equipped with a 3.5 g weight attachment contained within a cylindrical plastic coating (6 cm x 1 cm). A customized computer program controlled the vibratory stimulation and sampled the force platform data at 50 Hz. The vibrators had vibration amplitude of 1.0 mm and frequency of 85 Hz. Participants were instructed to focus on an image (6 cm x 4 cm) directly 1.5 m in front of them at eye level or keep their eyes closed depending on the test condition. The participants listened to calm classical music through headphones in order to reduce possible movement references from external noise sources and to avoid extraneous sound distractions. To ensure no prediction of the balance perturbation, all participants were naive to the stimulus and were not informed about the effect calf vibration would have on their balance. The following two assessment were performed in a randomized order, using a Latin Square design, by all subjects during three different test conditions: 1) 0.0%, 2) 0.06% and 3) 0.10% BAC:

- Vibration of the calf muscles with eyes closed (EC).
- Vibration of the calf muscles with eyes open (EO).

Before the vibration commenced, a 30 s control period of quiet stance was recorded. The vibratory stimulations were applied according to a pseudorandom binary sequence (PRBS) schedule (109) during four 50-s periods (period 1: 30-80 s; period 2: 80-130 s; period 3: 130-180 s; period 4: 180-230 s) of total 200 s. Thus, each trial was 230 s long. The PRBS schedule defined the periodicity of stimulation pulses, where each pulse and each interval between pulses had random time duration from 0.8 s up to 6.4 s (Figure 4), which yielded an FFT-validated effective bandwidth of the test stimulus in the region of 0.1–2.5 Hz. The PRBS sequence was selected because this randomized stimulation sequence is difficult to predict and therefore lessens the likelihood of pre-emptive responses (31). The selection of studying the recorded data in 50-s time intervals was based on prior studies on how postural control is gradually affected by prolonged randomized vibratory proprioceptive stimulation (81). A 5 minute rest period was given to the subjects between EO and EC tests. Posturography differs from most other sensory function assessments because it assesses the actual outcome i.e., the standing posture and its stability control, rather than attempt to assess peripheral or central function directly (110).

The segmental parts of the human body are interrelated. Due to this, calf vibration results not only in local postural alterations to the vibration site but also in a general modification of segmental and joint orientations remote from the vibration

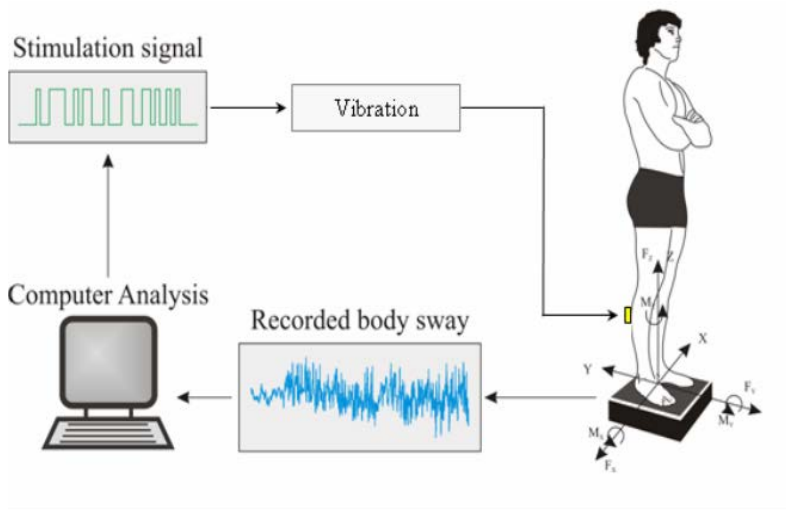
site (31, 111). These movements can be measured with kinematic analysis (see the Zebris section) and be analyzed to display the body movement coordination pattern, which is sometimes employed to evaluate the severity or rehabilitation status of a disorder (112).



**Figure 3:** Subject standing on a posturography force platform with Zebris position markers and calf vibrations attached.

### **Posturography - Measuring Torque**

Torque can be described as an energy that aims to create a rotational movement around a central rotational axis. This rotational energy is produced by the force pressure applied by the feet soles towards the force platform surface. The anteroposterior and lateral torque rotational axes are in level with the force platform surface.



**Figure 4:** Illustration of the posturography test procedure.

Torque ( $\tau$ ) can be calculated from the formula  $\tau = \text{CoP} \cdot \text{Fz}$ .

**CoP** represents the center of pressure (in meters) with distances in relation to the rotational axis.

**Fz** (vertical forces) will vary marginally due to body leaning or when the subject applies additional force to the surface to accelerate or decelerate a movement.

**Fz** can be calculated from the formula  $\text{Fz} \approx \mathbf{m} \cdot \mathbf{g}$ .

**m** represent the subjects mass (in kg)

**g** is the gravitational constant (9.81 in meter/s<sup>2</sup>).

The benefit of using torque instead of **CoP** is that it better represent balance stability. The variance of torque directly corresponds to the quantity of energy used to uphold standing (27, 113).

### Posturography - Torque variance

The torque variance of the anteroposterior (**Mx**) and lateral (**My**) torques (Figure 4) were calculated using the formula below. Anteroposterior direction is termed AP and lateral L.

$$(1) \quad \bar{\tau}_{AP} = \sum_{i=1}^n \frac{\tau_{AP}(i)}{n}$$

$$(2) \quad \tau(AP)_{\text{var}} = \frac{1}{n-1} \sum_{i=1}^n (\tau_{AP}(i) - \bar{\tau}_{AP})^2$$

$\bar{\tau}_{AP}$  denotes the average anteroposterior torque during the analyzed period.

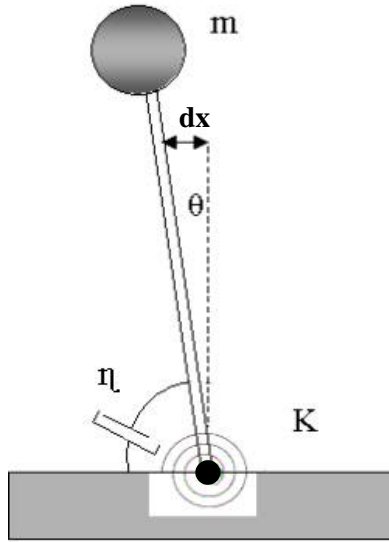
$\tau(AP)_{\text{var}}$  denotes the variance of the anteroposterior torque.

### **Posturography - Spectral separation of torque variance**

The torque variance was separated into three spectral categories. Variance of all registered torque was termed “Total”; variance of torque below 0.1 Hz was termed “low frequency torque variance”; and variance of torque above 0.1 Hz was termed “high frequency torque variance”. A fifth-order digital Finite duration Impulse Response (FIR) filter with components selected to avoid aliasing was used for spectral separation (114). Torque variance frequency above 0.1 Hz mainly show the fast corrective movements used to maintain balance. Frequencies below 0.1 Hz describe smooth corrective changes to the upright stance. The limit frequency was based on the cutoff frequencies of the visual and vestibular sensory systems which is about 0.1 Hz (115).

### **Posturography - Basis for anthropometrical normalization of torque variance**

The torque variance data were normalized to account for individual anthropometric variations of mass and height. Because of the biomechanical differences among taller or heavier subjects and therefor larger recorded torques, these differences must be adjusted for (116). The relationship between recorded torque by a force platform from a subject and that subjects’ mass and height is illustrated by the inverted pendulum model of human postural dynamics (Figure 5).



**Figure 5:** Illustration of the inverted body pendulum.  $T_{bal}$  represent balancing torque which is comparable to that achievable with a spring ( $K$ ) and a dashpot ( $\eta$ ).

If we assume that the inverted pendulum model is a good approximation of the human body during most movement made during posturography, the  $\tau$  (torque) recorded by the force platform can be described by the equation (3) below.

$J$  ( $ml^2$ ) is moment of inertia.

$l$  is the distance (meters) to the body's center of mass (**CoM**). The **CoM** is on average situated at about 55% of the subjects' height when normally built humans are standing.

$m$  is the mass (in kg) of the subject

$\theta$  represent the angle of the ankle joint.

$T_d(t)$  is the disturbance torque from the environment or measurement noise.

$$(3) \quad \tau(t) = J \frac{d^2\theta}{dt^2} + mgl \sin \theta(t) + T_d(t)$$

The first factor describes the torques produced from dynamical actions such as body acceleration and deceleration. The second factor describes the torques produced by the body's **CoM** position relative to the ankle joint. A leaning of the body, making the **CoM** no longer perfectly aligned in vertically direction with the ankle joint, produces this torques. This leaning is on average roughly 4 degrees forward when defined as an ankle joint angular rotation (see figure 5) in a normal

upright stance. Once transcription of formula (3) to formula (4) is done, it clarifies that the recorded torque is heavily dependent on the subject's mass ( $m$ ) and height ( $l$ ). The new formula also shows that the differences, caused by height, can be reduced but not completely excluded through normalization.

$$(4) \quad \tau(t) = ml\left(l\frac{d^2\theta}{dt^2} + g \sin \theta(t) + \frac{1}{ml}Td(t)\right)$$

Furthermore, since formula (2) contains a square element, normalization with the square of the height and mass of the subject is required to achieve unit agreement when normalizing torque variance values for anthropometrical differences.

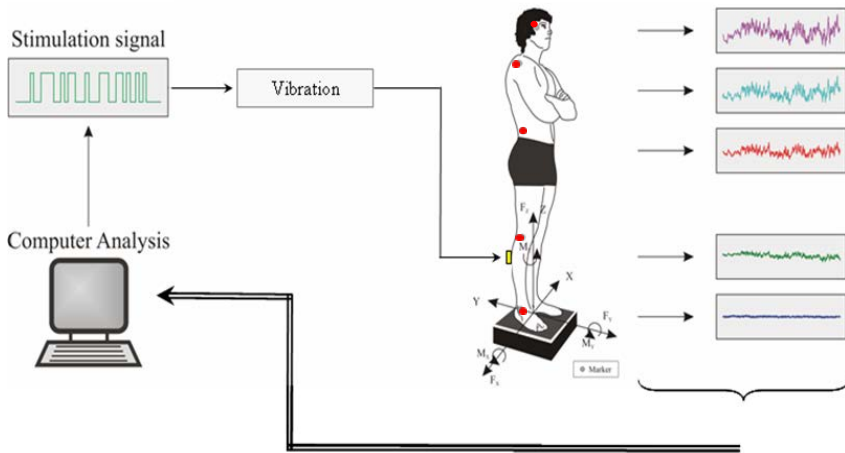
### **Posturography – measuring and analyzing adaptation**

Separation of the data into four time periods during the unpredictable perturbations allowed analysis of adaptive changes over time. The individual torque variance values for each period were first calculated. Thereafter, the quotient value between the first perturbation period (Period 1) and the last perturbation (Period 4) was calculated to describe the accumulated adaptation to the balance perturbation over time.

### **Zebris – assessing segmental body movements (Study V, VI)**

An ultrasound 3D-Motion Analysis system (Zebris™ CMS-HS Measuring System for 3D motion analysis) (Figure 6) measured the linear movements of five markers positioned at anatomical bony landmarks. The system sampled the position of the markers at 50 Hz and the five Zebris markers were attached on the right side of the participant facing the Zebris transmitter. The first marker (“Head”) was attached to the participant’s cheekbone (os zygomaticum), the second (“Shoulder”) to tuberculum majus, the third (“Hip”) to the spino-anterior of crista iliaca, the fourth (“Knee”) to the lateral epicondyle of femur, and the fifth (“Ankle”) to the lateral distal fibula head. The position of each marker was tracked in three directions, that is, anteroposterior, lateral, and vertical. The measurement resolution in all dimensions was 0.4 mm.





**Figure 6:** Illustration of the posturography assessment setup, simultaneously using a force platform and recording the body movements using a Zebri system. The positions of the Zebri movement markers are in red. The body movements were recorded simultaneously by both systems during quiet stance and while submitted to balance perturbations.

### Zebri - Linear body movement variance

The Zebri™ system recorded the movements of positions markers placed at the different body positions (head, shoulder, hip and knee). The linear body movement was quantified in terms of movement variance at each specific position. The formulas (5) and (6) below illustrate as example the calculations made for the head position marker.

$\bar{x}_{\text{Head}}(i)$  represents the marker's average linear anteroposterior position during the analyzed period.

$x(\text{Head})_{\text{var}}$  represents the variance of the head's linear anteroposterior movements during the analyzed period.

$$(5) \quad \bar{x}_{\text{Head}} = \sum_{i=1}^n \frac{x_{\text{Head}}(i)}{n}$$

$$(6) \quad x(\text{Head})_{\text{var}} = \frac{1}{n-1} \sum_{i=1}^n (x_{\text{Head}}(i) - \bar{x}_{\text{Head}})^2$$

### **Zebris - Basis for anthropometrical normalization of linear body movement variance**

When the body moves with a single link pendulum motion the amplitude of the linear movement will gradually be larger the higher up the body. This is presented by the formula (7) below.

$dx$  represent a linear distance in space moved by a zebris position marker. As formula (7) and figure 5 describes, will this distance be related to  $l$  (distance from the ankle joint to the marker position, which in turn is related to the subject's height) and  $\theta$  (ankle joint angle) (Figure 5).

$$(7) \quad dx = l \sin \theta(t)$$

Since the human body segments usually have the same relative proportions independently of the subject's height will taller humans be able to lean as much in degrees as shorter ones. Hence, although the angle of the ankle angular movement is the same, the size of the recorded linear anteroposterior and lateral movements will be affected by the height of the subject as formula (7) shows. Therefore, normalization with the subject's height has to be applied to compensate recorded linear movements for this anthropometrical variation. Moreover, since the formula (6) contains a square element, normalization with the squared height of the subject is necessary to achieve unit agreement with linear movement variance values.

### **Zebris - Analysis of body movement and segmental movement patterns**

In study VI the body movements were quantified by calculating the variance of the linear head, shoulders, hip, and knee movements in the anteroposterior and lateral directions. A movement variance value shows how much the body position marker has moved without being affected by average body leaning (31, 87, 117, 118)

In study V the concurrency between movements of different body segments was determined by calculating the correlation coefficients using the Spearman's rank correlation test between the hip and knee (hip-knee); shoulder and knee (shoulder-knee); head and knee (head-knee); shoulder and hip (shoulder-hip); head and hip (head-hip); and head and shoulder (head-shoulder) movements (31, 87, 119). These correlations were calculated for each subject on sample level, i.e., using 1,500 (30 s x 50) samples for quiet stance and 2,500 (50 s x 50) samples for each vibration period. A correlation analysis of body movements yield a value ranging from +1 to -1, where +1 represents that the movements are perfectly in phase with each other, 0 represents no relationship between movements and -1 represents that the movement are in perfect counter-phase with each other. When evaluated together, the correlation values provided information about the overall anteroposterior segmental body movement coordination pattern (31).

### **Assessing Spatial Orientation and Visual Dependence (Study III)**

During the spatial orientation test the subjects sat upright in a dark room with their heads fixed against a neck rest by straps (see Figure 7). A 15 centimeter long and 2 millimeter wide softly lit laser rod was projected on a wall 1.5m in front of them. The rod was rotated by the subject with a remote control four times to the perceived gravitational horizontal (the SVH) and four times to the perceived gravitational vertical (the SVV). The illustration of the SVH and SVV is based on the integration, interpretation, and processing of visual, vestibular, and somatosensory input in the central nervous system. By testing the perceived true horizontal and vertical using the SVH and SVV tests, it is possible to study the role of gravitational vestibular signals in determining the visual horizontal and vertical (120). The tests are considered to measure otolith function, but roles of the semicircular canals have not been ruled out (121, 122). Both the SVH and SVV tests can be used clinically to evaluate the vestibular otolith function in patients with vestibular lesions (123, 124).

The rod and frame test consist of the described SVH and SVV tests above except that there is a tilted square self-illuminating frame (100 x 100 cm) around the rod, tilted 20 degrees to either the right (CW) from the patients perspective or left (CCW) (125). The rod and frame test was used to measure visual field dependence (126, 127). Four measurements were made of the SVH and SVV with each frame tilt, and the mean was calculated. There is a substantial inter-individual variability of the visual field dependence. Subjects who trust vision rather than bodily referents are considered to be visual field dependent and move their perceived vertical or horizontal toward the frame tilt. Subjects who rely more on vestibular and proprioceptive information are visual field independent and show small or no deviations at all in the rod and frame test (127). Interestingly, inter-individual differences in postural performances have been strongly linked to visual field dependence (126, 127).

### **Spatial Orientation - Analysis**

Computer calculations generated the mean SVH and SVV. The mean of these two measurements was defined as the SVH-V since, in earlier studies, we have shown that test results of SVH and SVV are highly correlated (123). Two values were calculated. The 'SVH-V' calculated deviations in the clockwise (CW) or counter clockwise (CCW) directions (positive values indicating CW and negative values CCW deviations). The 'Abs. SVH-V', the absolute value of SVH-V, did not take into account whether deviations were in the CW or CCW direction. Subsequently, two values 'right frame tilt' and 'left frame tilt' were calculated, both taking into account whether deviations were in CW or CCW directions. In addition, the frame effect was calculated according to Nyborg and Isaksen (126). For each participant, the mean SVH-V deviation without the frame was subtracted from the mean deviations in the rod and frame tests, for both right (right frame effect) and left

tilted frames (left frame effect). Considerations were made in all these calculations whether deviations were in CW or CCW directions. The absolute sum of the right and left frame effect produced the total frame effect.

#### **Assessing oculomotor function (Study IV)**

The subject was positioned in an inclined chair in a completely dark room. The visual object, which the subjects were to follow, was a circular red target dot with a diameter of 3 mm projected onto a dark canvas screen (2 meters high and 3 meters wide) about 1.3 m in front of the subjects. The dot was generated by a diode laser contained within a manageable over-head console, permitting ideal individual vertical positioning. Eye movements were recorded by electronystagmography (ENG) using a bipolar recording technique (Figure 7). Two Ag/AgCl ENG-electrodes were placed about 1 cm from the outer brim of the eyes measuring horizontal eye movements. Two electrodes were fixed below and above the left eye to measure vertical eye movements and blinking. Finally, one ground electrode was also attached on the mid-forehead.



**Figure 7:** Examination of eye movement using ENG-electrodes.

The eye movement recordings were primarily filtered by an analogue 340 Hz low-pass filter and sampled on-line at 200 Hz. Before each trial, a calibration routine was performed to ensure that electrical ENG signals corresponded correctly. The

error limits were set to less than 1 degree at the 30 degrees amplitude to right and left eye movements within the range of  $\pm 30$  degrees amplitude. The eye movements were calibrated in the horizontal direction in a separate saccade calibration program with amplitudes of 10 degrees, 20 degrees and 30 degrees to the left and right. In the vertical direction, the calibration amplitude was set with reference to the effects of eye blinks so these artifacts were recorded without exceeding the measurement scales. A custom-made computer program (Vestcon™) controlled the visual target projection, calibration and sampled the ENG data. Once collected, the computer program automatically analyzed the ENG data according to the methods described below.

### **Assessment and data analyze of smooth pursuit eye movements**

Subjects were instructed to fixate on a dot projected onto a screen and follow its movement as accurately as possible without turning their head or moving their eyes before the target had moved. Movements of the head were prohibited by a custom-made headrest. The smooth pursuit dot moved horizontally with a constant velocity from side to side, with a range of  $\pm 30$  degrees of the visual field. Thus, it moved a distance of 60 degrees between (+) 30 degrees to the right and (-) 30 degrees to the left. The test started with that the dot was stationary straight ahead (0 degrees) for 2 seconds. Thereafter the dot jumped to +30 degrees to the right and this position was maintained for 1 second. Then, the visual dot moved according to the following sequence of velocities: 10, 20, 30, 40, 40, 30, 20 and 10 degrees/second. The smooth pursuit eye movements were tested four times at each velocity level, twice for smooth pursuit movements directed from right to left, and twice for movements directed from left to right. When the visual dot reached the maximum amplitude, i.e.,  $\pm 30$  degrees either to the right or left, the position was maintained for 1 second before the next smooth pursuit movement began in the opposite direction. The total test time for the smooth pursuit test was 135 seconds. Before the analysis of the smooth pursuit data, the recorded ENG data was low-pass filtered at a cut-off frequency of 15 Hz. Thereafter, the data was deemed to attain the velocity of the eye movements for each dot movement.

The recorded smooth pursuit latency was defined as the time passed between the start of target movement until the velocity of the recorded eye movement exceeded 5 degrees/second. The most common reaction to the start of the smooth pursuit target movement was an initial short pause followed by a short period of quicker than target smooth pursuit to catch up with the visual target. Sometimes even catch-up saccades occurred. The analysis method used was designed to handle both these kinds of responses. The calculated latency time was ignored if the latency was shorter than 0.1 second or longer than 0.6 second.

The average smooth pursuit gain was calculated by that the analysis procedure first identified and deleted time phases where the recorded eye movements were

assumed to be saccades. This was attained by deleting all recordings where the eye movement velocity exceeded the velocity of the visual dot by 40 degrees/second. Succeeding this filtration, the average eye movement velocity for each remaining time phases was calculated using linear regression. If the calculated average eye movement velocity within a time phases was below 5 degrees/second, the time period was deemed to contain no smooth pursuit eye movements and was deleted. The smooth pursuit gain value was calculated by dividing the average eye movement velocity by the dot velocity value.

Recently, a method based on quantifying the ability to maintain accurate smooth pursuit movement was found to be particularly sensitive in detecting performance deterioration caused by sleep deprivation (128). This method, the smooth pursuit velocity accuracy, for each dot movement was calculated as the percentage of time the smooth pursuit eye movement velocity was within the dot velocity boundaries of less than 20% absolute error from the visual target velocity during eye movements. A somewhat similar approach but restricted to 20 deg/s stimulus velocity has previously been suggested by Bergenius (129). It should be pointed out that both methods describe a composite effect on smooth pursuit.

#### **Assessment and data analysis of saccadic eye movements**

The settings and calibration before testing were identical to smooth pursuit recordings as were the test directives. In the pro-saccade evaluation, testing began after a 5 second phase where the target dot was stationary straight ahead (0 degrees). Afterward, the visual dot jumped stepwise horizontally according to the following sequence of amplitudes:  $\pm 10$  degrees,  $\pm 20$  degrees and  $\pm 30$  degrees, generating saccades of a total range of, respectively 20 degrees, 40 degrees and 60 degrees amplitude. The dot appeared for 1.5 seconds at each position. The saccades were tested 10 times at each of the amplitudes, five times for saccades from right to left, and five times for saccades from left to right. Between each sequence step, the visual dot was projected straight ahead for 5 seconds. The total test time for the saccade test was 66 seconds. Preceding the analysis of the saccadic data, the recorded ENG data was low-pass filtered at a cut-off frequency of 70 Hz. Afterward, the data was deemed to obtain the velocity of the eye movements during each individual target dot movement.

The saccade latency was measured as the time passed from the beginning of dot movement until the recorded eye movement velocity exceeded 80 degrees/second. The calculated latency was deleted if the latency was below 0.1 second or above 0.6 second. The saccade was also deleted if the duration of the saccade was shorter than 25 milliseconds, as it was regarded a measurement artifact.

Peak saccade velocity was calculated by identifying and deleting time phases where the recorded eye movements were slower than 80 degrees/second and where saccades were shorter than 25 milliseconds. Afterward, in the remaining time

phases where saccades were found, the 25 milliseconds phase (e.g., 5 samples) where the saccade velocity was highest during the saccade was determined. Then the average saccade velocity during this 25 millisecond phase was calculated. If the subject made numerous saccades to reach the target dot movement, the saccade with the highest peak saccade velocity and with the largest amplitude was selected.

Another parameter was the saccade accuracy for each target movement which was calculated as a quotient value in percent between the amplitude of the largest eye movement saccade (if several saccades were made), divided by the movement amplitude of the visual dot target reference. To conclude whether there was any general ratio decrease between peak saccade velocity and saccade amplitude due to alcohol intoxication, average individual quotients between peak saccade velocity divided by saccade amplitude were calculated using data from each saccade target amplitudes.

### **Assessing sensitivity (Study II)**

The sensitivity of the low threshold mechanoreceptors of both feet was measured in sober state in all participants. Vibration perception (rapidly adapting mechanoreceptive sensation) of the feet plantar surface was measured using a biothesiometer electronic device (Model EG electronic BioThesiometer, Newbury, Ohio, USA). The biothesiometer produced a 120 Hz vibration of varying amplitude (in micrometers). The vibration was applied to the plantar surface of the first distal phalanx (big toe), the fifth distal phalanx (little toe), the first proximal phalanx (base of big toe), the fifth proximal phalanx (base of little toe) and the tuberosity of calcaneus (heel). Subjects were questioned to indicate to the examiner whether they were able to feel the vibration “Yes” or “No” (130). Three readings in ascending intensity and descending intensity were made until the subject could no longer sense the vibration. The mean was then calculated.

Tactile sensitivity (slowly adapting mechanoreceptive sensation) was measured with a Semmes-Weinstein pressure aesthesiometer (Semmes-Weinstein Mono-filaments, San Jose, USA). The aesthesiometer contained of 20 nylon filaments of equal length but with variable diameter. The filaments were applied to the plantar surface of first distal phalanx (big toe), the fifth distal phalanx (little toe) and the tuberosity of calcaneus (heel). Subjects were informed that when the filament was placed on any of the positions, they should report to the examiner whether they felt it on the “big toe”, “little toe” or “heel.” Tactile sensation threshold was determined by exerting suprathreshold filaments primarily, then applying thinner and thinner filaments until the subject could no longer sense them (130). The examiner then applied thicker filaments until the filament again was detected. The touch threshold was determined from three ascending and three descending steps and is presented as Semmes-Weinstein size (sw).

# Statistical methods

In all investigations, except III, the data were analyzed with a multifactorial statistical method, which consists of two statistical evaluation steps of the data. The first step was to perform a multifactorial univariate **General Linear Model analysis of variance (GLM ANOVA)** on the calculated values. The second step was post hoc pair-wise analyses (**Wilcoxon**) of the significances found in the first step GLM ANOVA evaluation. The multifactorial analysis was performed both on the data from the quiet stance recordings and on the data from the four 50-s periods of vibratory proprioceptive balance perturbations. Nonparametric statistical tests (Wilcoxon) were used in the evaluation because the **Shapiro-Wilk** (Study I, II, IV, VI) and **Kolmogorov–Smirnov** (Study IV) tests revealed that the obtained data sets analyzed with pair-wise statistics were not normally distributed and normal distribution could not be obtained by log transformation.

## **GLM univariate ANOVA (Study I, II, IV, V, VI)**

The interactions on the recorded values during quiet stance and during balance perturbations was analyzed by the GLM univariate ANOVA (General Linear Model univariate Analysis of Variance) analyze. The GLM reveals whether the outcome might be influenced by certain combinations of factors. The main factors included in the GLM analyses for each investigation were:

**Study I:** Alcohol, Vision, Period, Direction

**Study II:** Alcohol, Vision, Period, Sensation

**Study IV:** Alcohol, Target Velocity, Target Amplitude

**Study V:** Alcohol, Vision, Period

**Study VI:** Alcohol, Vision, Period, Direction



The statistical main factors in study I, II, IV, V and VI were defined as:

- Effects of alcohol intoxication dosage ('**Alcohol**': 0.0%, 0.06% or 0.10% BAC; degrees of freedom (d.f.) 2)
- Availability of visual information ('**Vision**': eyes closed or eyes open; d.f. 1)
- Direction of recorded torque variance ('**Direction**': anteroposterior or lateral; d.f. 1)
- Plantar sensation ('**Sensation**': exact)
- Period, when applicable, of vibration period index ('**Period**': periods 1–4; d.f. 3)
- Effects of smooth pursuit velocity ('**Target Velocity**': 10, 20, 30 or 40 degrees/second; d.f. 3)
- Effects of saccade amplitude ('**Target Amplitude**': 20, 40 or 60 degrees; d.f. 2)

Log-transformed torque variance values (Study I, II, VI) were used in the GLM ANOVA analysis because the torque variance values did not have a normal distribution profile when tested with the Shapiro–Wilk statistical test (131). In study IV, oculomotor performance was based on the analysis of rightward and leftward smooth pursuit and saccadic eye movements pooled together since no direction differences were noticeable in the statistical analysis (128, 132).

The GLM model accuracy was evaluated by testing (with Shapiro-Wilk) the model residual for normally distributed. In a couple of cases, noted in the respective result tables, this gave negative results suggesting a somewhat lower reliability for the statistical result. However, the GLM model accuracy was in all evaluations approved when the analysis was performed on log-transformed movement variance values. In the GLM Anova analysis, p-values <0.05 were considered statistically significant.

#### **Wilcoxon matched-pairs signed-rank (post-hoc) (Study I, III-VI)**

The Wilcoxon matched-pairs signed-rank test (exact sig. 2-tailed) (131) was used for the post hoc statistical comparisons between paired observations, different test conditions and for analysis of the significances found in the GLM Anova evaluation.

Wilcoxon test was used for comparisons between values obtained under different alcohol dosages (i.e., 0.0, 0.06 and 0.10% BAC) with eyes closed and open (Study I, V, VI); for analysis of variations over time in study V and for comparisons between values obtained under different alcohol dosages on all parameter values obtained in study IV.

The correlation changes between quiet stance and period 1 (Study V) were evaluated to determine how the assessed parameters were initially affected by the

balance perturbations evoked by vibratory proprioceptive stimulation compared to the activity during quiet stance (89). The correlation changes (Study V) and torque variance change (Study I) between period 1 and period 4 were evaluated to determine how the assessed parameters were affected by repeated vibratory stimulation, quantifying the possible accumulated effects of adaptation (89).

In Study VI quotients were calculated between the movement variance values at 0.06% BAC divided by the values at 0.00% BAC, respectively, between the values at 0.10% BAC divided by 0.06% BAC to describe the destabilization rates between these different BAC levels. Wilcoxon pair-wise tests were then used to determine whether the destabilization rates were significantly different between 0.00% BAC and 0.06% BAC compared with between 0.06% BAC and 0.10% BAC. The statistical analysis was carried out with Bonferroni correction compensating for multiple comparisons.

### **Spearman's correlations (Study II, III, IV, V)**

A Spearman's rank correlation test (131) was used in study V to calculate the correlation coefficients between the movements at each measured body position. Additionally, correlation was used in study IV and V to evaluate the correlation between subjective VAS scores of drunkenness and the body movement coordination pattern (Study V) respectively to the eye movement parameters (Study IV). In study II correlation analysis was performed between mechanoreceptive sensitivity scores and anteroposterior torque variance at 0.00%, 0.06% and 0.10% BAC. In the analysis, p-values <0.05 were considered statistically significant.  $P < 0.1$  was considered as indications of trends.



# The investigations

## **Blood Alcohol Concentrations during the investigations:**

- At the intended 0.06% BAC level the average measured BAC were 0.057% (standard error mean (SEM) 0.001%) and the time between subjects finished drinking and when starting with either posturography or eye movement tests were on average after 83 min (SEM 5 min).
- At the intended 0.10% BAC level the average measured BAC were 0.101% (SEM 0.002%) and the time between subjects finished drinking and when starting with either posturography or eye movement tests were on average after 84 min (SEM 4 min).
- At the control 0.00% BAC level the tests were performed after roughly the same time (76 min SEM 4 min) between subjects finished drinking and when starting with either posturography or eye movement tests. This was made to maintain the integrity of the blind study design.

The general objective for the thesis was to combine the findings made in each of six separate investigations done to observe the multiple parallel sensory and motor control effects of acute alcohol intoxication. We categorize the results as described below throughout the thesis:

- **Dose-dependent alcohol effects:** The dose dependent alcohol effects (i.e., how much alcohol do you have to drink to achieve certain effects) on balance and eye movements.
- **Direction-specific alcohol effects on body sway:** Direction specific effects of alcohol intoxication (i.e., if alcohol affects the anteroposterior or lateral body sway more) on postural control.
- **Time-dependent alcohol effects and adaptation:** Time dependent effects of alcohol intoxication including stability deterioration over time. Effects of alcohol intoxication on adaptation, i.e., whether someone gets better as a perturbation is repeated.
- **Alcohol effects on the body segments and body movement pattern:** Alcohol-related changes of the multi-segmental movement pattern.
- **Alcohol effects on visual contribution:** Visual influence during alcohol intoxication.
- **Multiple alcohol effects and interactions:** How certain factors in interaction with each other may influence recorded activity.
- **Subjective evaluation of alcohol intoxication:** The subject's subjective feeling of drunkenness.

# Study I: Effects of 0.06% and 0.10% blood alcohol concentration on human postural control

**Subjects:** 25 healthy subjects (13 women and 12 men) with a mean age of 25.1 years (range 19-41 years) participated in the study.

**Study design:** Subjects ingested alcohol to reach pre-specified BAC (blood alcohol concentration) levels of 0.00% (i.e. sober), 0.06% and 0.10%. BAC was measured with a real-time breath analyzer. Effects of alcohol intoxication on postural control (balance) were examined with posturography during 230 seconds of quiet stance and calf vibration. Tests were performed with either eyes open or closed. Torque variance was divided into total, high frequency (above 0.1 Hz) and low frequency (under 0.1 Hz). High frequency represents fast corrective body movements to maintain balance and low frequency describe smooth corrective changes to the upright stance.

## **Results:**

***Dose-dependent alcohol effects:*** Postural stability (torque variance) worsened significantly during quiet stance and during perturbations while under alcohol intoxication ( $p < 0.001$ ) (Figure 8). The instability engendered by alcohol intoxication was largest at 0.1% BAC and the stability best while sober (0.0%). Postural stability was only slightly poorer at 0.06% BAC compared to sober. Beyond 0.06% BAC, postural stability decayed considerably.

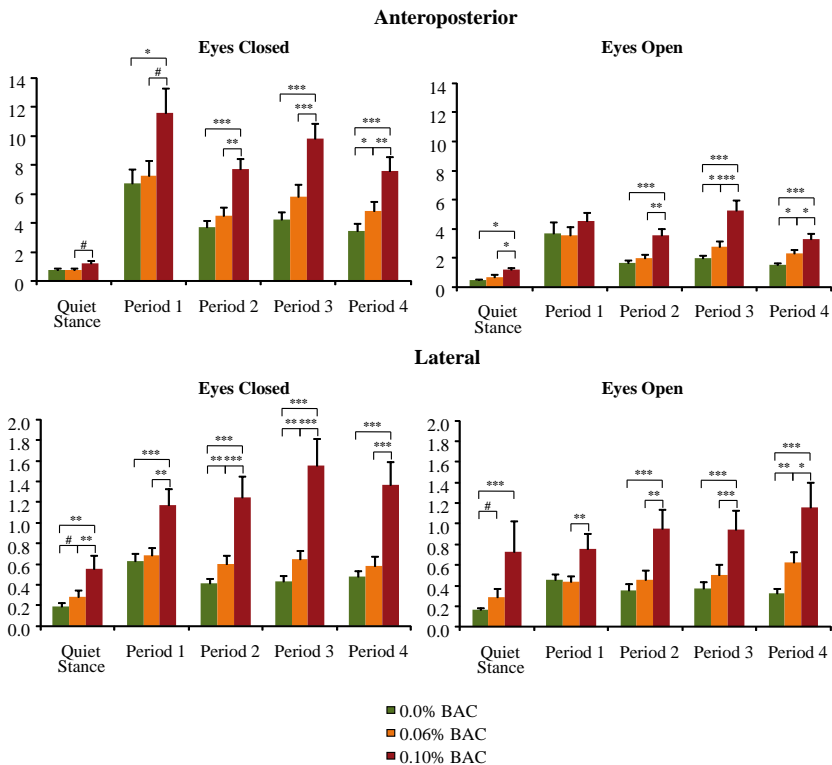
***Direction-specific alcohol effects on body sway:*** The direction-specific alcohol effects decreased stability more in lateral direction than in anteroposterior direction with both eyes open and closed. Torque variance was larger in anteroposterior compared to lateral direction.

***Time-dependent alcohol effects and adaptation:*** The interaction between alcohol and period (time) indicate time-dependent effects, that sustained exposure to repeated balance perturbations (on total and low frequency spectra) enlarged the alcohol-related destabilization ( $p \leq 0.005$ ). Simultaneously, with the time effects, postural adaptation was gradually broken-down, particularly in lateral direction and especially in the low frequency body sway spectra, when the balance perturbations were repeated at 0.06% and 0.10% BAC. At 0.1% BAC with eyes open there were significant ( $p \leq 0.017$ ) declined in stability in high and total frequency torque variance indicating that adaptation was totally abolished.

***Alcohol effects on visual contribution:*** Vision improved all stability during perturbations and mainly, except low frequency spectra, during quiet stance. Vision also decreased postural sway more in anteroposterior direction than lateral in both total and high frequency torque variance ( $p < 0.001$ ).

**Multiple alcohol effects and interactions:** There were two interactions between vision-direction and direction-period (time) which illuminate that the high frequency torque variance body sway was helped significantly less over time by vision in lateral compared to anteroposterior direction.

**Conclusions:** Alcohol had profound deteriorating effects on human postural control. The effects were dependent on the alcohol dose ingested, the direction of the body sway and the time duration of the balance challenge (i.e., increased intoxication effects over time). The alcohol dose effect was non-linear. Hence, the maximal effects of alcohol intoxication on physiological performance might not be evident initially, but may be revealed first when under sustained sensory-motor challenges. Adaptation was deteriorated or even abolished. Vision aids balance in intoxicated subject but is not as effective as when sober.



**Figure 8:** Normalized torque variance values ( $[\text{Nm}/(\text{Kg}\cdot\text{m})]^2$ ) on y-axis from tests with eyes closed and eyes open (mean and SEM) for (A) total torque variance in anteroposterior direction and (B) total torque variance in lateral direction. X-axis shows time periods. Note the difference in scales. In the figures, # denotes  $p < 0.05$ , \* denotes  $p < 0.0167$ , \*\* denotes  $p < 0.01$  and \*\*\* denotes  $p < 0.001$ .

## Study II: Mechanoreceptive sensation is of increased importance for human postural control under alcohol intoxication

**Subjects:** 25 healthy subjects (13 women and 12 men) with a mean age of 25.1 years (range 19-41 years) participated in the study.

**Study design:** Subjects ingested alcohol to reach pre-specified BAC (blood alcohol concentration) levels of 0.0% (i.e. sober), 0.06% and 0.1%. BAC was measured with a real-time breath analyzer. Effects of alcohol intoxication were examined with posturography during 230 seconds. Balance was examined unperturbed or perturbed by calf vibrations and with either eyes open or closed. The posturography results (i.e. torque variance) were divided into total, high frequency (above 0.1 Hz) and low frequency (under 0.1 Hz). Plantar cutaneous mechanoreceptive sensation was measured with a pressure aesthesiometer for slowly adapting (tactile sensitivity) and with a biothesiometer for rapidly adapting (vibration perception) receptors. The correlation between sensation from the mechanoreceptor and measured balance torque variance was calculated. Only anteroposterior torque variance is considered here since the main direction of movement from calf vibration is in that direction.

### **Results:**

***Dose-dependent alcohol effects:*** Vibration perception and tactile sensation were important during standing. Persons with poor vibration perception and poor tactile sensation had larger postural instability. The relationship between postural control and vibration perception (Figure 9) at 0.1% BAC during perturbations had significant correlations mainly in total and high frequency spectrum torque variance with eyes closed. There were significant interactions between both vibration perception and tactile sensation and alcohol dose suggesting increased influence of mechanoreception on balance with rising alcohol level. Tactile sensation did not correlate significantly with torque variance.

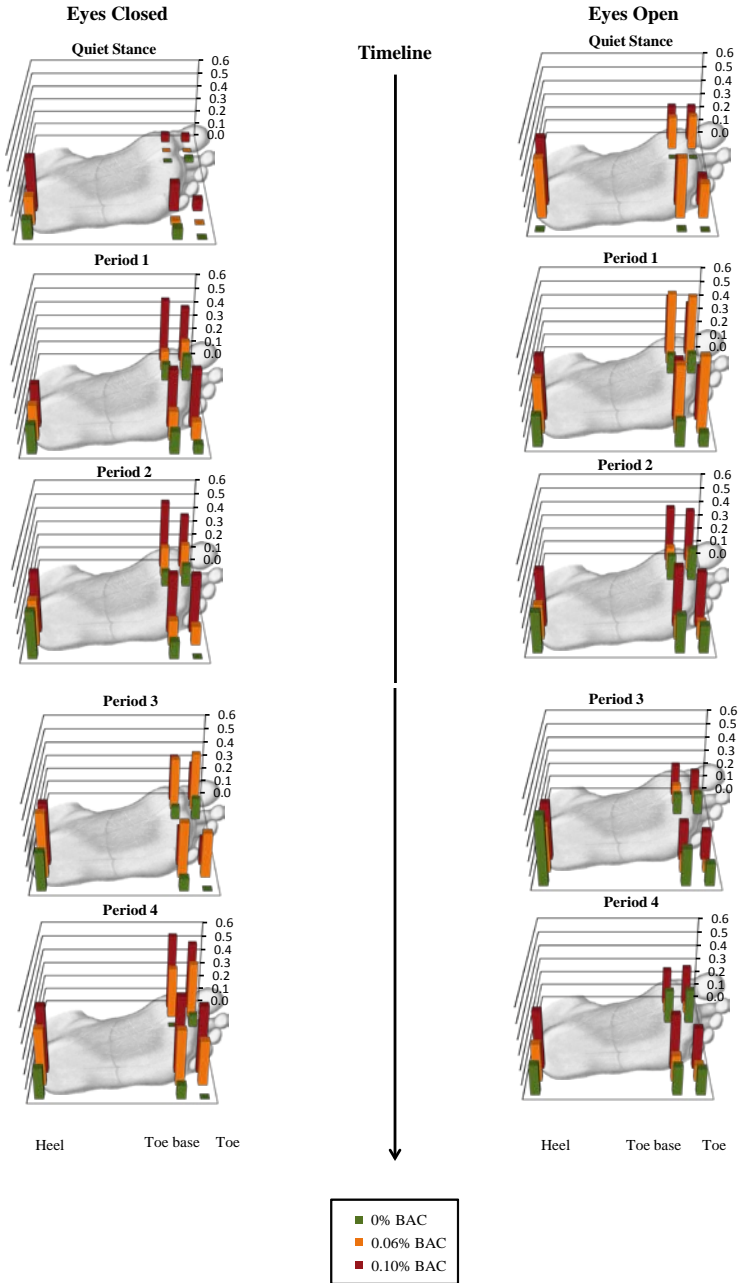
***Time-dependent alcohol effects and adaptation:*** At 0.06% correlations between postural control and vibration perception increased in period 3 and 4 on total and low frequency spectra with eyes closed. At 0.06% correlations indicate strong relationship between vibration perception and torque variance on mainly total and low frequency spectra (some in high) in only period 1 with eyes open. At 0.1% high frequency torque variance express strong relationship between vibration perception and torque variance during the entire test with eyes closed. With eyes open at 0.1% vibration perception mainly correlated with total and high frequency torque variance during period 1 and 2 and thereafter only moderate relationship was found.

*Alcohol effects on visual contribution:* During perturbations, especially in high frequency spectra, there was an interaction between vision and both vibration perception and tactile sensation. When there was no visual feedback (eyes closed), the subjects relied more upon the sensory information provided by the foot soles in terms of pressure and weight distribution compared to standing with eyes open.

**Conclusions:** The subjects' ability to handle balance perturbations during acute alcohol intoxication was strongly dependent on an accurate mechanoreceptive sensation and efficient CNS sensory re-weighting.



Correlation Torque variance vs Vibration sensation



**Figure 9:** Correlation coefficient values (y-axis) between vibration perception under the feet at various feet positions and total torque variance with eyes open or closed at different BACs. A timeline from the top to the bottom of the side illustrates the time from quiet stance until period 4. Higher correlation coefficient values illustrate a stronger relationship between postural control and vibration perception, i.e., a stronger relationship between those who had poorer vibration perception also had poorer postural control. The figures show that during Quiet Stance with Eyes Closed, the relationship between postural control and vibration perception was weak, though somewhat stronger at higher levels of alcohol intoxication (i.e., 0.10% BAC). However, the balance perturbations strengthened the relationship between postural control and vibration perception so that the relationship was clearly significant in period 4 at 0.10% BAC and was present at lower alcohol doses also (0.06% BAC). With Eyes Open, similar effects were found during balance perturbations, except that the relationship between postural control and vibration perception was significant at both levels of alcohol intoxication initially (i.e. 0.06 and 0.10% BAC). However, when reaching the last 50 s period of the test (period 4), the relationship had clearly weakened to levels well below the ones found with eyes closed, though somewhat stronger with higher alcohol doses (i.e., 0.10% BAC).

## Study III: Increased visual dependence and otolith dysfunction with alcohol intoxication

**Subjects:** 24 healthy subjects (13 women and 11 men) with a mean age of 25.1 years (range 19-41 years) participated in the study.

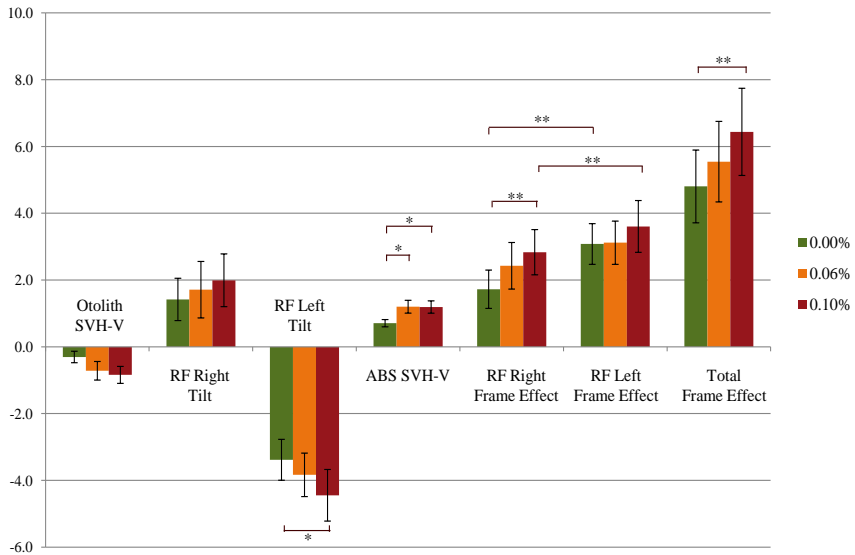
**Study design:** Subjects ingested alcohol to reach pre-specified BAC (blood alcohol concentration) levels of 0.00% (i.e. sober), 0.06% and 0.10%. BAC was measured by a real-time breath analyzer. The subjects were tested with spatial orientation tests to evaluate the ability to perceive the subjective visual horizontal (SVH), subjective visual vertical (SVV) and the visual field dependence. The SVH and SVV are considered to measure the otolith function (i.e. function of utricle and saccule).

### **Results:**

**Dose-dependent alcohol effects:** Absolute SVH-V (i.e. absolute SVH-V at both Clockwise (CW) and Counter Clockwise (CCW) tilt together) deviations were larger at both 0.06% ( $p=0.021$ ) and 0.1% ( $p=0.026$ ) BAC comparing to sober (Figure 10). SVH-V alone was not significant. The alcohol effect was more pronounced in CCW than in CW direction.

Deviations of left frame tilt were significantly ( $P=0.019$ ) greater at 0.1% compared to 0.0% BAC and right frame tilt also increased but not significantly. The total frame effect was significantly ( $p=0.002$ ) larger at BAC 0.1% than when sober. The frame effect was greater when compared the left to the right tilted frames at 0.0% ( $p=0.01$ ) and at 0.1% ( $p=0.003$ ).

**Conclusions:** The frame effect results indicate increased visual field dependence during alcohol intoxication. When visual and vestibular/proprioceptive information were contradictory, alcohol seemed to stimulate a reweighting in balance control to an increased visual dependency. During alcohol intoxication, subjects were more prone to rely on visual information due to the sensory reweighting. These results propose that alcohol intoxication down-weights vestibular and proprioceptive information when determining the vertical and horizontal orientation.



**Figure 10:** Y-axis illustrates mean deviations (in degrees) and standard deviations for the subjective visual horizontal and vertical (SVH-V). The spatial orientation tests with right and left frame tilts, the absolute (ABS) SVH-V, the right frame effect, the left frame effect, and the total frame effect. At SVH-V, RF Right tilt and RF Left tilt a positive value indicate clockwise and negative values counter clockwise deviations. In the figures, \* denotes  $p < 0.05$  and \*\* denotes  $p < 0.01$ . The deviation of the SVH-V and the visual field dependence increased with increasing BAC. Deviations were greater when the frames were tilted in the CCW direction than in the CW direction

# Study IV: Oculomotor deficits caused by 0.06% and 0.10% blood alcohol concentrations and relationship to subjective perception of drunkenness

**Subjects:** 25 healthy subjects (13 women and 12 men) with a mean age of 25.1 years (range 19-41 years) participated in the study.

**Study design:** Subjects ingested alcohol to reach pre-specified BAC (blood alcohol concentration) levels of 0.00% (i.e. sober), 0.06% and 0.10%. BAC was measured by a real-time breath analyzer. The aim was to investigate deficiencies in eye motor performance.

Oculomotor performance was evaluated by electronystagmography including measurements of smooth pursuit gain, smooth pursuit latencies, saccade velocity, saccade accuracy and saccade latencies. Two novel parameters were also calculated, smooth pursuit velocity accuracy (i.e. the percentage of time the smooth pursuit eye movement velocity was within less than 20% absolute error of the visual target velocity boundaries) and the relationship (i.e. ratio) between peak saccade velocity vs. saccade amplitude, further describing oculomotor performance.

## **Results:**

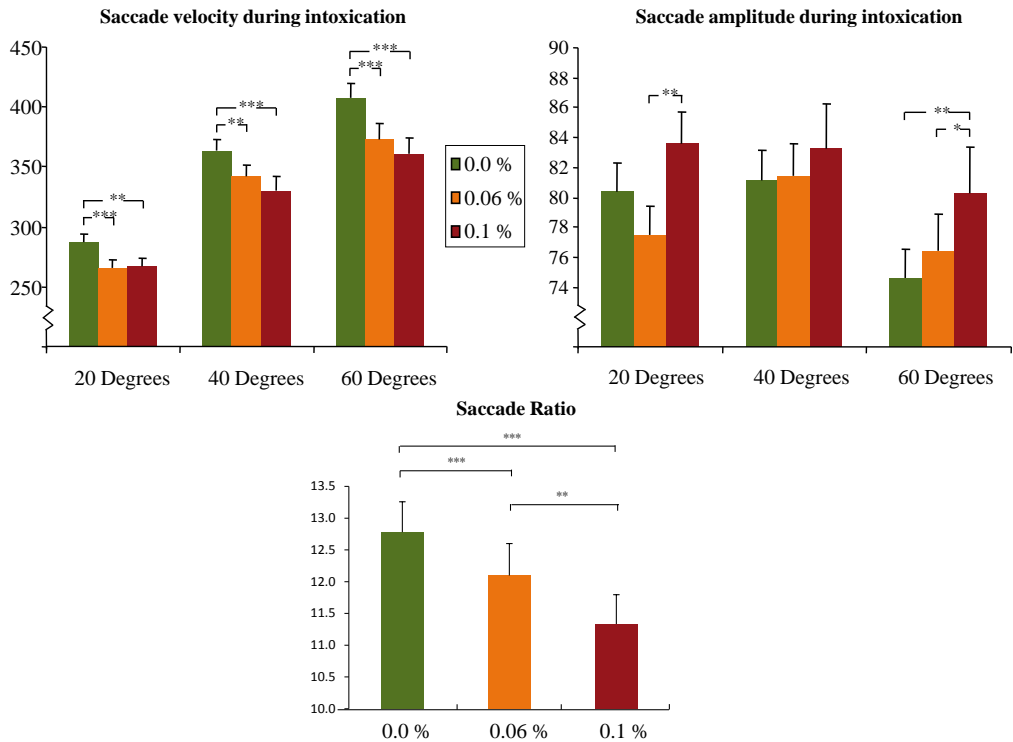
***Dose-dependent alcohol effects:*** At 0.06% BAC, alcohol started to deteriorate smooth pursuit velocity accuracy ( $p < 0.001$ ) (Figure 12), smooth pursuit gain ( $p < 0.025$ ) (Figure 12) and saccadic velocities ( $p < 0.01$ ) (Figure 11). At 0.10% BAC, saccade accuracy, at the 60 degree saccade, increased ( $p < 0.01$ ) (Figure 11) and the average saccade latencies increased ( $p = 0.004$ ). The ratio between saccade velocity and saccade amplitude decreased significantly (Figure 11) under alcohol intoxication due to worse capacity for saccades to reach high peak velocities ( $p < 0.001$ ). The average smooth pursuit gain was more accurate during slower target velocities, however it was easier to maintain correct smooth pursuit velocity during higher velocities ( $p < 0.001$ ). The average smooth pursuit latencies differences were not significant between BAC levels.

***Multiple alcohol effects and interactions:*** There was an interaction between alcohol intoxication and gain at higher smooth pursuit target velocities ( $p = 0.024$ ).

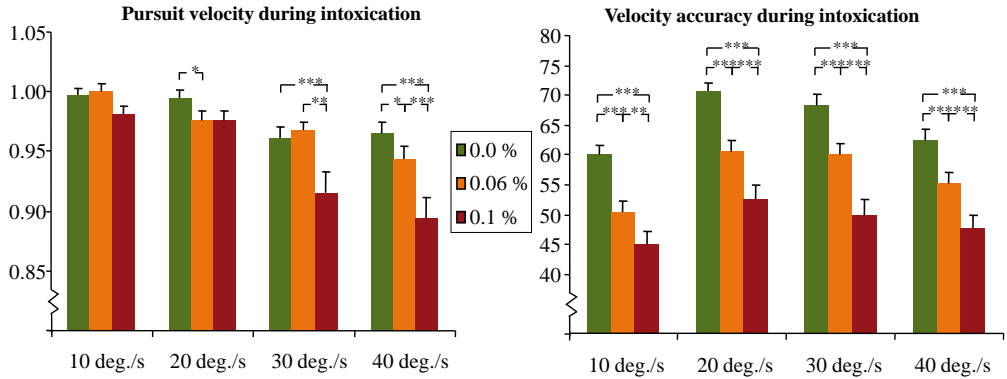
***Subjective evaluation of alcohol intoxication:*** Self-perceptions of drunkenness correlated well with changes in smooth pursuit velocity accuracy, especially during the slower velocities ( $p < 0.001$ ), but poorly with the other oculomotor parameters. The VAS scores, where 1 = “sober” and 10 = “extremely drunk”,

presented on average 1.1 (SEM 0.1) for the 0.0% BAC, 2.5 (SEM 0.3) for the 0.06% BAC and 4.5 (SEM 0.4) for the 0.1% BAC.

**Conclusions:** Many of the smooth pursuit and saccade characteristics were altered dose dependently by alcohol, so they became worse as BAC was higher. The alcohol induced oculomotor deficits, which were found already at 0.06%, might have safety implications for tasks that rely on visual motor control and visual feedback.



**Figure 11:** Saccade velocity: Saccadic eye movement velocity (degrees/sec) on y-axis (mean and SEM) for three saccade amplitudes. Saccade amplitude: Average saccade accuracy in percentage on y-axis (mean and SEM) during different levels of BAC. A value of 100 represents perfect saccade accuracy whereas values below 100 represent short saccades (hypometric). In the figures, # denotes  $p < 0.05$ , \* denotes  $p < 0.025$ , \*\* denotes  $p < 0.01$  and \*\*\* denotes  $p < 0.001$ . Saccade ratio: Alcohol intoxication changed the relationship between saccade velocity and saccade amplitude, and these observed changes were due to a diminished capacity, over the entire range of saccade amplitudes, for saccades to reach high peak velocities. The individual average saccade ratio between saccade velocity and saccade amplitude, during 20, 40 and 60 degree measurements, are presented on the y-axis. In the figures, # denotes  $p < 0.05$ , \* denotes  $p < 0.025$ , \*\* denotes  $p < 0.01$  and \*\*\* denotes  $p < 0.001$ .



**Figure 12:** Pursuit velocity: Gain values (mean and SEM) on the y-axis for four target velocities during different levels of BAC. A value of 1.00 represents perfect average smooth pursuit gain and a value below 1.00 represent that the average smooth pursuit velocity was below the target velocity.  
 Velocity accuracy: Average smooth pursuit velocity accuracy values on the y-axis, representing the percentage of time the smooth pursuit velocity were within the target velocity boundaries of less than 20% absolute velocity error compared with the visual target velocity (mean and SEM), during different levels of BAC. A value of 100 represents that the smooth pursuit eye movement velocity were always within the boundaries of less than 20% velocity error.

# Study V: Alcohol intoxication at 0.06 and 0.10% blood alcohol concentration changes segmental body movement coordination

**Subjects:** 25 healthy subjects (13 women and 12 men) with a mean age of 25.1 years (range 19-41 years) participated in the study.

**Study design:** Subjects ingested alcohol to reach pre-specified BAC (blood alcohol concentration) levels of 0.00% (i.e. sober), 0.06% and 0.10%. BAC was measured by a real-time breath analyzer. The aim was to investigate whether the intended alcohol intoxication affected the segmental movement pattern during unperturbed standing or perturbed by calf vibrations with eyes opened or closed. Furthermore, to determine if movement pattern adaptation was affected by alcohol and whether the subjective feeling of drunkenness correlated to the used movement pattern. Body movements were measured by an ultrasound 3D-Motion analysis system (Zebris) and the individual segmental movements were registered at five locations (ankle, knee, hip, shoulder and head). Since calf vibration mainly induces body movement in an anterior-posterior path we only considered the responses in this direction.

## **Results:**

***Time-dependent alcohol effects and adaptation:*** In sober and intoxicated subjects, with eyes open or closed, correlations between segments mainly increased at onset of vibrations. However, hip-knee and head-knee correlations with eyes closed were not affected by vibrations, which maintained the same posture assumed during quiet stance. This indicates more rigid movement pattern and is interpreted as a sort of segmental adaptation. However, there was no evidence of adaptation when sober or intoxicated.

***Alcohol effects on the body segments and body movement pattern:*** Alcohol intoxication induced no significant effect on the general movement pattern in unperturbed stance. There was a change in the movement pattern when intoxicated at 0.10% BAC, during persistent balance perturbations (e.g. period 4) with eyes closed, correlations between head-knee ( $p = 0.005$ ), shoulder-knee ( $p = 0.002$ ) and hip-knee ( $p = 0.005$ ) movements were significantly smaller (Figure 13) i.e., regulation of postural stability from the knees. There were no significant differences with eyes open.

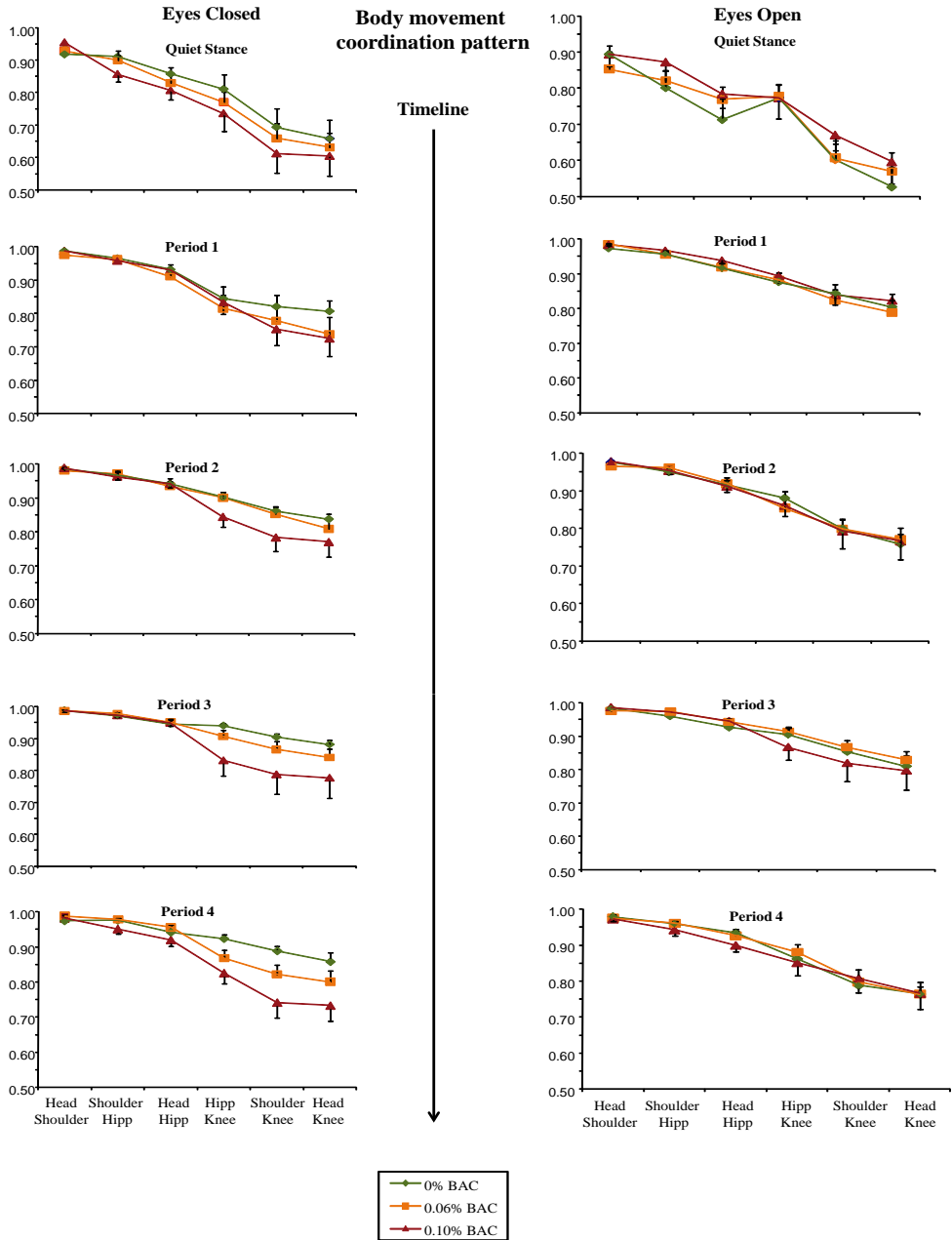
***Alcohol effects on visual contribution:*** Correlations between head-shoulder, shoulder-hip and head-hip movements were larger when vision was not available. This proposes increased rigidity above the waist with eyes closed.



***Multiple alcohol effects and interactions:*** There were statistical interactions between BAC level and vision on correlations between shoulder-knee ( $p = 0.02$ ) and head-knee ( $p = 0.032$ ). The correlations were smaller during intoxication and with eyes open.

***Subjective evaluation of alcohol intoxication:*** When subjects marked lower VAS values (e.g. felt more sober) during perturbations the body movements of head, shoulder and hip were more correlated. No effects were found during quiet stance.

**Conclusions:** The correlations between segments, when intoxicated, indicate that knee movements became significantly less correlated to the other measured body movements during persistent perturbations with eyes closed. This suggests that a normal movement pattern could not be sustained and that the knees increasingly had to be used for stability regulation to ensure safe stability, i.e., a knee strategy. The inability to relate subjective drunkenness with lower body movement and to the demand to change the knee movement pattern as an effect of alcohol intoxication could be a contributing factor to falls.



**Figure 13:** Body movement coordination pattern during quiet stance and during calf vibration in periods 1–4 for eyes closed and eyes open at 0.0, 0.06 and 0.10% BAC. Correlation coefficient (y-axis) between body segments (x-axis).

## Study VI: Blood alcohol concentration at 0.06% and 0.10% causes a complex multifaceted deterioration of body movement control

**Subjects:** 25 healthy subjects (13 women and 12 men) with a mean age of 25.1 years (range 19-41 years) participated in the study.

**Study design:** Subjects ingested alcohol to reach pre-specified BAC (blood alcohol concentration) levels of 0.00% (i.e. sober), 0.06% and 0.10%. BAC was measured by a real-time breath analyzer. The aim was to investigate whether alcohol intoxication affected the body movements during unperturbed and perturbed upright stance and to analyze how alcohol affects the ability for sensorimotor adaptation. Linear body movements were recorded by an ultrasound 3D-Motion analysis system at five locations (ankle, knee, hip, shoulder, and head) during quiet standing and during balance perturbations with eyes closed or open. Vibrations were generated from pseudorandom pulses of calf muscle vibration.

### **Results:**

***Dose-dependent alcohol effects:*** The linear movement variance both during quiet stance and perturbations was increased by alcohol (Head movement illustrated in Figure 14). Alcohol effects at 0.1% during perturbations were mainly highly significant ( $p < 0.001$ ).

***Direction-specific alcohol effects on body sway:*** Linear movement variance was significantly larger ( $p < 0.001$ ) in anteroposterior than lateral direction in quiet stance and during perturbations in both sober and intoxicated state.

***Time-dependent alcohol effects and adaptation:*** With increased BAC, there was sensorimotor adaptation deterioration. In fact, in lateral direction at 0.06% BAC with eyes open and at 0.1% BAC with both eyes open and closed the adaptation was abolished. At 0.1% with eyes open the deterioration (or loss of adaptive capacity) was significant for hip ( $p = 0.015$ ), shoulder ( $p = 0.011$ ) and head ( $p = 0.016$ ).

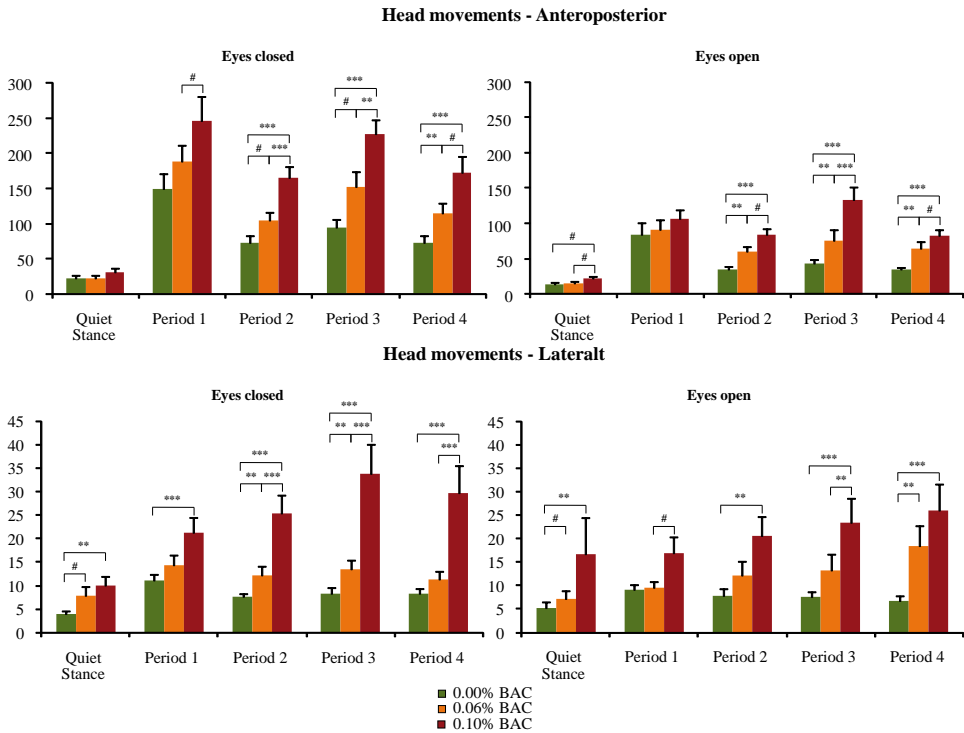
***Alcohol effects on the body segments and body movement pattern:*** During quiet stance in anteroposterior direction alcohol intoxication did not change the movement pattern (movement at each position was synchronized, i.e., a single-link). Conversely, with eyes open, the upper body demonstrated a more pronounced destabilization between 0.06% and 0.1% BAC than between 0.0% and 0.06% BAC. In lateral direction with eyes closed, the alcohol destabilization was less affected in the upper body between 0.06% and 0.1% BAC than between 0.0% and 0.06% BAC. Conversely, alcohol destabilization was more affected in the lower body between 0.06% and 0.1% BAC than between 0.0% and 0.06% BAC.

In lateral direction with eyes open, alcohol intoxication did not change the movement pattern (movement at each position was synchronized, i.e., a single-link). In both directions during perturbations the destabilization was greater between 0.06% and 0.1% BAC than during 0.0% and 0.06% BAC. The knee movement amplitude decreased noticeably ( $p < 0.05$ ) with eyes closed between period 3 and 4 in anteroposterior direction at 0.1% BAC. The movements of all other measured body parts were similarly increased over time.

***Alcohol effects on visual contribution:*** Vision decreased linear movement variance but provided a weaker contribution to postural control during alcohol intoxication during perturbations. No effects were found during quiet stance. At the upper body a statistically significant interaction between vision and direction indicated that vision helped to stabilize anteroposterior direction more than lateral.

***Multiple alcohol effects and interactions:*** There was a progressive decline in stability in lateral direction compared to anteroposterior indicated by the interaction between direction and time (denotes period in the article). The significant interaction between alcohol and time indicate that there was a non-linear increase of alcohol effects on linear body movement variance over time in both directions. Lateral direction was affected most and had by the end of the test, for example, 381% larger values at 0.1% BAC than sober with eyes closed.

**Conclusions:** The effects of alcohol became greater with increasing alcohol intoxication and larger in latter time periods, especially in lateral direction. Alcohol intoxication at 0.06 and 0.10% BAC caused a complex multifaceted deterioration of human postural control and diminishes adaptive capabilities. The knee movement had a changed roll in the end of the balance test which suggests that the system, which regulates postural control, altered the movement pattern. A more complex multi-segmented movement pattern was necessary to cope with the effect of alcohol intoxication.



**Figure 14:** Normalized anteroposterior and lateral linear movement variance values ( $[(\text{mm}/(\text{m}))^2]$ ) of the head (mean and standard error of the mean) with eyes open or closed. Note the difference in scales. The figures present the statistical findings made in the post hoc evaluation of the main factor Alcohol, the interaction between Alcohol x Period, and the interaction between Direction x Period. In the figures, # denotes  $p < 0.05$ , \* denotes  $p < 0.017$ , \*\* denotes  $p < 0.01$  and \*\*\* denotes  $p < 0.001$ .

# General discussion

## Methodological considerations

### **Test procedure**

Stringent procedures were maintained during data capture to avoid bias. Each subject acted as their own control, attended three separate, randomized, single-blind assessment days, which were executed and instructed identically. Timing before which the subject was allowed to leave was governed so not to give any unnecessary dosage clues.

### **Exclusion criteria to avoid over-consumers**

We used the AUDIT questionnaire as a screening test for excessive alcohol. A drawback with questionnaires is that they require the subject to answer honestly. Revealing any level of alcohol intake can be embarrassing, owing to social stigmas. Except for asking and checking the form, there were no real possibilities for the study administrators to validate that the information given in the AUDIT questionnaire were correct. Audit is a well-validated questionnaire and we used generally accepted limits when rating the alcohol consumption. The World Health Organization, classifies AUDIT scores of over 8 as possibly hazardous drinking and scores over 15 as possibly harmful drinking. The AUDIT limit was set to 15 or higher for subject exclusion. Given that about 20% of the Swedish inhabitants are hazardous drinkers, we opted against setting the AUDIT limit to 8 to include a general population.

### **Alcohol masking**

It is inevitably difficult to create a placebo control to a substance with a characteristic taste and smell as alcohol. We used elderflower juice after a small pilot study on different mixers. We also considered the option of masking the opposite way i.e. to put some alcohol on the brim of every drinking glass. However, we found that test setup more risky because the taste of alcohol might instigate subjective expectations of being drunk (133). A later study by Gundersen et al found that during intoxication of 0.08% BAC, the neural activation decreased in dorsal anterior cingulate cortex and in prefrontal areas (134). The opposite effect was found during expectations of intoxication in sober subjects, i.e. showed increased activation of the same areas. These findings may support our approach to use taste masking.

### **Alcohol dosing**

Intake of alcohol via drink ingestion was chosen to mimic the normal method of intake among non-alcohol abusers. This method was made possible by the very exact real-time breath analyzer used in the study, which provided precise and repeatable measures of alcohol level. The Evidenzer is a “state of the art” breath analyzer, which is used by the Swedish police agency to catch drunk driving because of its high accuracy and reliability. Because of the strict BAC monitoring, we could ensure that all subjects were tested in the descending phase of intoxication as opposed to the ascending which would skew results owing to the Mellanby effect. Alcohol has more detrimental effects in the ascending phase, so the effects of alcohol intoxication described in the thesis probably under-estimate the worst effects alcohol can have at the assessed level.

### **Measuring mechanoreceptive sensation**

Whilst tactile sensitivity contributes to postural control (showed by a significant factor effect in GLM ANOVA), there was no correlation between tactile sensitivity and torque variance. Tactile sensitivity was measured with a Semmes-Weinstein pressure aesthesiometer, which comprises 20 monofilaments differing in thicknesses that increment irregularly. These monofilaments transfer different pressures onto the skin. Given their irregularity, tactile sensitivity scores could be imprecise i.e., the real sensitivity could fall between two monofilaments. This could explain no significant correlation between tactile sensitivity and torque variance. For research purposes, a better assessment device may have to be designed which allows the user to assess tactile sensation with higher resolution and which assess tactile sensation using a linear scale (like the BioThesiometer used for vibration perception).

One factor which could be debated is that alcohol intoxication could alter plantar mechanoreceptive sensation. The sensation was measured once, in sober state prior to the study. If there were any alcohol-related effect on plantar mechanoreceptive sensation, this was not taken into account. However, hitherto we are not aware of reports on a systemic reduction of sensitivity of cutaneous mechanoreceptors in acute alcohol intoxication.

### **Analyzing balance**

Posturography is probably the most common method to assess stability of a subject's upright stance. Several different methods are used to quantify the stability recorded during posturography. The most common measures relates to the center of pressure position, expressed as sway path or sway area. In this thesis, an energy concept was instead used, relating the stability recorded to the physical effort required. Further, spectral separation was used to illustrate the energy used within different frequency spectral, with the purpose to analyze the composition of postural responses. The flexibility of postural control can also be investigated by

quantifying the adaptation to repetitive events. However, this requires fairly long test duration, including several repeated events to allow all parts of the learning and consolidation process to be recorded and quantified. Moreover, an apparent finding in several studies was that the performance during the initial 50s was much better than during the latter parts of the stability tests while intoxicated, thus, sustained exposure to a challenging sensorimotor task may be handled differently over time. Hence, postural control is not a static function but a dynamic process, which is affected by time-variant beneficial (e.g., adaptation) and detrimental (e.g., fatigue) changes acting on different time scales. Accordingly, posturography tests should be designed so they can assess the properties of these different phases and aspects of a flexible dynamic sensorimotor function.

Disturbed coordination in motor tasks is a well known effect in acute alcohol intoxication (42). Disturbed coordination between movements of limbs and body segments may reduce postural control and could thus be a part of the effect of alcohol on balance. To assess such coordination disturbances we needed to assess segmental movements. We recorded segmental movements with a 3D motion analysis system and analyzed both size of the body movements and determined the segmental movement patterns, the latter using a novel approach where we statistically correlated the movements of different body positions compared to each other's spatial location. This explored inter-segmental movements and made it easier for multi-segmental estimations. Large measurement noise could potentially distort or bias movement pattern analysis bases on correlations. However, the numerous high correlation values close to 1 show that noise was not a determining factor in the studies included in this thesis.

### **Analyzing eye movements**

Voluntary eye movements as smooth pursuit and voluntary saccades may reflect both alertness, attention and to a certain level, composite cerebral function (135, 136). Eye movements were evaluated using standardized procedures using electronystagmography. Additionally, we employed measurements of two rather novel parameters, smooth pursuit velocity accuracy and the relationship (ratio) between peak saccade velocity vs. saccade amplitude.

The smooth pursuit velocity accuracy parameter returns an approximation about the capacity to maintain a smooth pursuit eye movement velocity close to stimulus velocity, as given in percentage of stimulus speed. Interestingly, both in study IV regarding alcohol intoxication effects and in a prior study investigating the effects of sleep deprivation (128), the smooth pursuit accuracy parameter was the most sensitive measure of an affected oculomotor function. Therefore, as evidenced in two independent studies and previously indicated in studies (46, 137), one of the first signs of an affected oculomotor function might be an inability to maintain accurate control of smooth pursuit movements over longer periods of time. It



should be pointed out that a similar approach was applied by Bergenius in 1984 (129) where early computer analysis of smooth pursuit and that the accuracy is a composite approximation of total performance that includes both effects of CNS function, attention and cognitive set.

The saccade ratio, between peak saccade velocity and saccade amplitude of individual saccades was also evaluated as a reflection of the main sequence velocity – accuracy trade off for saccadic eye movements (128, 138). Previous reports have shown a relatively fixed relationship between the saccade amplitude and saccade velocity up to about 15–20 degrees amplitude. Above these saccade amplitudes, the relationship changes in a non-linear manner (128, 139). However, it has been found that sleep deprivation changed the relationship between saccade velocity and saccade amplitude, the ratio values evidencing decreased maximum velocities for the saccades when the saccade amplitude effects were factored in (128). The saccade analysis parameter (ratio of saccade velocity and amplitude), illustrating the velocity vs. amplitude relationship changes, proved in most cases to be more sensitive in detecting the detrimental effects caused by alcohol intoxication than an individual analysis of the traditional parameters saccade velocity and saccade accuracy.

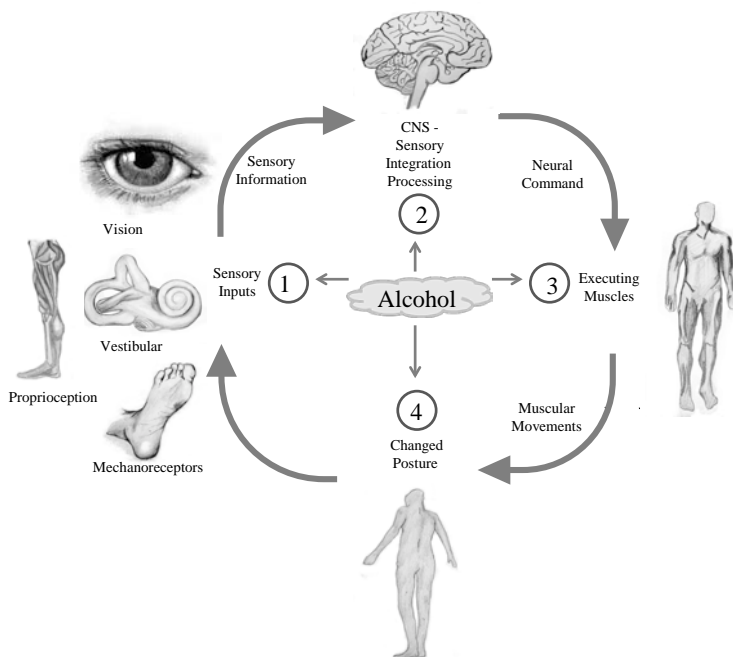
### **Correlation analysis between movements of body segments**

The correlation method for segmental body movements offers an opportunity to describe complex movement patterns in an objective way (31). Methods based on correlation analyses have also previously been used to explore multi-segmented movement coordination (140, 141).

Still, it is important to not regard any kind of correlation variations as indication of poor stability or stability-enhancing changes of postural control. The movement pattern has to be estimated from what can be expected as normal under the present test situation. During unperturbed stance, a more “relaxed” movement pattern with less synchronized movement pattern can be expected and should be regarded as normal. However, during provoking balance perturbations, produced by vibratory calf stimulation, findings propose that healthy individuals systematically use a more rigid single-link pendulum movement pattern. This pendulum pattern could be regarded as the normal movement pattern for that situation (31). Subsequently, systematic deviations from this movement pattern may be regarded as a sign of an alternative movement pattern necessary for the situation. Postural stability could not be maintained and strategic actions have been taken to maintain stability.

# Effects of alcohol on balance and orientation

Acute alcohol intoxication has multiple, simultaneous, effects on the human sensory systems, spatial orientation and postural control (Figure 15). Normally, subjects use their sensory receptors, i.e. vision, vestibular, proprioception and mechanoreception, to gather information which is integrated and processed in CNS to achieve postural control, also termed balance (22, 23, 26). This is a continuously ongoing process including feedforward and feedback mechanisms to constantly hold the intended body position or control body movements (27). Although the test subjects in intoxicated state at 0.06% or 0.1% BAC, largely had access to similar though somewhat disrupted sensory information, they seemingly used it in a significantly different and less effective way (Study I). This poorer balance and handling of sensory information may cause accidents and falls with risk of subsequent injuries (3).



**Figure 15:** Schematic illustration over postural control and alcohol influence. The numbers in the figure are described in the sections below.

## *The sensory inputs*

Alcohol affected the impact or importance of the different sensory receptor systems in postural control (1- See Figure 15). That is; the amount body sway reduced or increased, by adding or subtracting or alternatively disturbing an input from the different sensory systems differed when subjects were sober and when they were intoxicated. Hence, demonstrating an effect of alcohol to alter and impair the utilization of the normal sensory inputs.

For example, correct visual information is especially important when the validity of vestibular and somatosensory information is impaired such as in patients with bilateral vestibular loss (142) or when the stability is challenged (87, 118). However, even though vision mostly increased postural stability, this enhancement was of lesser magnitude during alcohol intoxication (Study I, VI), as previously described also by Boonstra et al. (143). A remarkable observation in study I and VI was, that when intoxicated not only was the stability reduced more over time while standing with eyes open than with eyes closed, the decline was so large so it approached a state where the stability in lateral direction was almost as poor with eyes open as with eyes closed. These findings raise questions about why particularly vision gradually loses so much of its positive effect as information source to postural control. Whilst eye movements are not directly indicative of the distortions of visual information used for the regulation of standing postural control, study IV illustrates how several important properties of eye motor control were severely impaired by alcohol intoxication. Previous studies have reported both general saccadic and smooth eye pursuit movement slowing, onset latency increase and decreased peak saccade velocity (45-49, 144). The presented results verify that the oculomotor functions are affected by alcohol concentrations as low as 0.06% BAC, though the control of smooth pursuit movements seemed to be more affected than the control of saccades (study IV). The observed decline in smooth pursuit gain is in agreement with previous reports (47, 145) (46). These properties of eye movement control will also have implications on the information provided by vision, e.g., whether moving objects can be maintained in focus and whether the eyes can follow and determine movements of the own body relative the surroundings without producing disorienting retinal slips. Moreover, poor eye movement control can impair visual functions which regulate head position whilst moving (i.e., visual stabilization) or in visually-demanding tasks which necessitate eye movements (i.e., driving). Vision was especially poor at enhancing the stability in lateral direction during intoxication (Study I, VI). Lateral threats to stability, through a sudden push or sideslip, may therefore be particularly difficult to handle without falling if intoxicated.

The vestibular system registers the position and movement of the head and the direction of gravity (52, 124). It is known that alcohol affects the vestibular receptors by changing the density of the cupula and endolymphatic fluid. Thus, it is reasonable that during alcohol intoxication, the CNS chose to rely more on visual information than vestibular (study III).

Afferent information from cutaneous mechanoreceptors of the soles of the feet is conveyed to the CNS where it assists in maintaining postural control (58-60, 146). When heavily intoxicated, the subjects that had higher sensation thresholds and hence lesser mechanoreceptive vibration perception (i.e. higher stimulus amplitude needed before the subject felt the vibration) had predominantly much poorer balance stability compared to those with better vibration perception sensation, especially during balance perturbations with eyes closed (study II).

### *CNS – Integration and processing of sensory input*

The CNS integrates and processes the sensory information and subsequently initiates motor programs to maintain balance (67, 72, 73) (2- See Figure 15). However, the normal improvement of balance over time, i.e. adaptation (81), during repeated perturbations was diminished or entirely absent during alcohol intoxication (Studies I and VI). However, the properties of this negative process might be difficult to determine objectively because the recorded responses during posturography can be presumed to be a summation of several continuously ongoing processes operating under different time frames. Several of these processes, including adaptation, might be affected by alcohol in a multitude of ways. Hence, while the positive effects of adaptation are mostly manifested during the initial 100 seconds of balance perturbations (147), the effects of detrimental processes due to alcohol intoxication may manifest themselves first when the immediate changes due to adaptation have subsided. This hypothesis is supported as sensorimotor control and movement pattern changes were exaggerated during the last 100 seconds of the 230 second long stability tests (Study I, II, V, VI). An alternative theory however, would be that besides a reduced adaptation there might be a decreased ability to uphold the adaptation during alcohol intoxication.

Another possible explanation for the time-dependent effects and also the decrease in adaptation could be fatigue and deteriorating attention toward the end of the postural tests. Since alcohol is known to affect attention, performing an attention-demanding task might be particularly difficult, especially if that task has to be executed over a prolonged period of time. Following alcohol intoxication, the accompanying decrease in attention may have led to slower or incorrect sensory integration, which affected the postural adaptation processes, or the ability to maintain adaptation. Although vibratory perturbations per se may briefly increase attention or motivation in both animals and humans (148), the findings in study I

and VI suggest that this attention increase was sustained only during an initial short period of the stability tests. Consequently, the recorded deficits under alcohol intoxication were relative to the performance as sober, the smallest during the first 50s period of the stability tests. Hence, inability to uphold an attention-demanding complex sensorimotor task such as postural stability could be an indication of that alcohol intoxication may have more complex effects than often assumed.

A second possible explanation for the time-dependent detrimental effects could be a shortcoming of the postural control system to handle the more demanding integration of information from partly malfunctioning sensory systems over prolonged time. This complex situation may result in an uncertainty on which sensory information to trust as a basis for motor control and adaptive processes. Gundersen et al found that during alcohol intoxication of 0.08% BAC, the neural activation decreased in dorsal anterior cingulate cortex (dACC) and cerebellum when participants performed demanding tasks (149). The dACC is important for cognitive control as decision making, error monitoring, response inhibition and working memory. As the cerebellum is strongly associated with continuous balance and adaptation (83, 88), an alcohol-related impairment of the cerebellum could explain the results of poor adaptation in studies I and VI. The results of Gundersen et al. also concur with Belmeguenai and Diener et al. who propose that acute alcohol intoxication seems to affect the function of the cerebellum (42, 80) by blocking cerebellar parallel-fibre long-term depression (42).

When the calf muscles are vibrated, there is a proprioceptive illusion that the muscle is being stretched. This increases the demand on the remaining, appropriate, sensory receptors to compensate through sensory reweighting (150). Likewise, Maurer and colleagues (151) have indicated, through mathematical modeling, that a disturbance in vestibular information and ankle proprioception causes reweighting to plantar mechanoreceptive sensation. A significant interaction was found between alcohol intoxication and plantar sensation on torque variance, although plantar sensation was within normal limits among subjects. This suggests that the contribution of plantar mechanoreceptive sensation becomes of larger importance for postural control when intoxicated and that CNS up-weights information from the mechanoreceptive sensors, particularly during high BAC (study II).

Moreover, the spatial orientation tests showed that alcohol intoxication caused an increase in visual field dependence. Subjects relied more on their visual information than on vestibular gravitational information (study III). Earlier studies by Wollacott et al. discovered an increased reliance on visual information when alcohol intoxicated, especially when proprioceptive information is simultaneously perturbed (12, 18). During acute alcohol intoxication, the vestibular gravitational spatial orientation sensory input could not override the visual signals when

exposed to confounding visual information i.e. the tilted frame. The results might though be equivalent to the visual re-weighting in balance control that occurs with weakened vestibular function due to other causes than alcohol ingestion (i.e., disease) (152, 153).

### *Executing muscles*

The execution motor response represents the strength, quickness and the coordination of the muscular movement (3- See Figure 15). Study I, II, V and VI have not evaluated each of these muscular properties but instead gathered these into evaluation of a holistic balance function. Balance worsens gradually non-linearly during increasing alcohol intoxication. These effects on balance were unanimous through it was evaluated with two different methods i.e., force platform (posturography) and segmental body movements (Zebris).

### *Changed posture - Biomechanical constraints and imbalance*

Investigation of segmental body movements showed that intoxicated subjects, especially at 0.10% BAC, use a movement pattern with knee movements less correlated to upper body movements during proprioceptive disturbances by calve vibrations while standing with eyes closed. This suggests that a different movement coordination pattern had to be used to compensate for the destabilizing effects of alcohol (4- See Figure 15). A change of proprioceptive information arising from the calf causes both local postural changes and widespread modifications of segmental body movements. It also changes the joint orientation remote from the vibrated site. Therefore, vibration often results in movement at different levels of the body due to multilevel segmental coordination (111, 154) (study VI). This discovery further illustrates the increased stability regulation initiated from the knees is necessary whilst intoxicated, termed the knee strategy. This proposes that a different movement coordination pattern had to be used to compensate for the destabilizing effects of alcohol. Similar movement pattern changes have previously been found to be an indicator of balance difficulty (87, 117, 155). Moreover, this knee strategy was absent in quiet standing. Comparable to these results, previous studies of alcohol on static balance have revealed only very small balance deficits in quiet standing at approximately 0.04% (38) and below 0.08% BAC (34).

The biomechanical design of the human body offers a multitude of multi-segmented movement patterns to handle stability challenges. Principally, two movement strategies have been defined in the literature, the ankle strategy and the hip strategy. With the movement coordination analysis methods, i.e. the correlation analysis (31, 87), there is evidence for a third strategy, a knee strategy. This strategy might be an intermediate state between the classic ankle strategy used when perturbed by vibratory stimulation to the calf muscles and a hip

strategy which is possibly the strategy used when stability is greatly threatened. The alteration to a multi-segmented movement pattern is used when an increase in whole body rigidity is insufficient to maintain stability (32, 156). The knee strategy described offers the advantage that independent correctional movements can be produced at two separate joints, both at the ankle and at the knee whereas the upper body segments still move in a simple concurrent manner. An analogous use of a knee strategy during balance perturbations, as found during acute alcohol intoxication, has been found in elderly with known balance deficits (87).

### *Subjective feeling of intoxication*

Alcohol intoxication presents itself as a sometimes sought after subjective feeling of drunkenness. This subjective factor is vital as it warns the affected subject of impaired capacity but at the same time reflect the decreased cognitive ability. The latter may lead to risky behavior, endangering the individual or others. If individuals sense that they are not impaired after they have ingested alcohol, they might involve themselves in potentially hazardous activities, such as car driving. On the other hand, when performing alcohol intoxication studies, subjective expectancy of certain effects after believing to have drunk alcohol may have substantial impact on the results (133). For example, sober subjects may intentionally or unconsciously behave as intoxicated if they think they have consumed alcohol.

Here, oculomotor parameters correlated poorly with the subjective feeling of drunkenness. This is in line with several reports (48, 145) whereas other studies report at least some correlations (49, 157). However, the VAS scores correlated highly significant with the smooth pursuit velocity accuracy values, particularly at 10 degrees/s and 20 degrees/s stimulus velocities (Study IV).

When studying the body segments there was some evidence of a relationship between subjective VAS drunkenness scores and the body movement coordination pattern. When subjects marked lower VAS values (e.g. felt more sober) during perturbations the body movements of head, shoulder and hip were moved more concurrent with each other. One possible explanation is that one's own feeling of drunkenness and instability might predominantly be associated with the inability to maintain a stable movement pattern of the upper body.

# Implications

When humans are profoundly intoxicated, falls and disturbed motor control are evident and expected. At lower levels of intoxication, such as those investigated here, one is more prone to assume that falls and accidents are a result of the cognitive effects of alcohol and the accompanying loss of judgment. This thesis reports clear but perhaps less evident effects of alcohol on postural control as well as on eye motor control and hence orientation and visual ability. Such effects, may very well contribute to falls and traffic accidents but also to other accidents. This strongly both advocates and supports a restrictive policy toward alcohol intake in situations where accidents may occur and there is a demand on even low level motor skills.

Acute alcohol intoxication impairs postural control, particularly during balance challenges and particularly when they are repeated and when motor learning is required for counteraction. So, alcohol intoxication might not have immediate effects on performance, yet these may present itself with repeated challenges. Therefore, activities requiring motor learning during extended periods may be dangerous during alcohol intoxication. For example, alcohol intoxication may be the cause of accidental falls presenting to emergency departments (158).

The correlation analyses of the segmental coordination pattern in Study V may offer a novel approach for detecting postural deficits caused by drugs or diseases acting on the CNS and on receptor systems used for maintaining postural control.





# Conclusions

- Alcohol had profound deteriorating effects on human postural control also at the lowest 0.06% BAC level tested. The detrimental effects recorded were dependent on the alcohol dose ingested, the frequency and direction of the body sway and for what duration the subjects' had been submitted to the balance challenges (Paper I).
- Postural adaptation was deteriorated or even abolished during intoxication (Paper I).
- Vision enhances balance during intoxication but is not as effective an enhancer of stability as when sober (Paper I).
- Without the help of vision, subjects with poorer vibration perception had poorer postural stability during the latter part of the perturbation sequence when intoxicated (Paper II).
- Mechanoreceptors were of increased importance when visual feedback was absent (Paper II).
- The subject's ability to handle balance perturbations during acute alcohol intoxication was strongly dependent on individuals' mechanoreceptive sensation and efficient CNS sensory re-weighting (Paper II).
- When visual and vestibular/proprioceptive receptor information were contradictory, alcohol intoxicated subjects seemed to reweight their spatial orientation reference to increasingly rely on vision (Paper III).
- Many of the smooth pursuit and saccade characteristics were decreased dose dependently by alcohol (Paper IV).
- Increased subjective perception of drunkenness was significantly correlated to decreased ability to maintain a steady smooth pursuit eye movement for longer times during intoxication (Paper IV).
- The segmental movement pattern analysis suggested that intoxicated subjects had increasingly more difficulties in maintaining a normal movement pattern during the latter part of the balance perturbation sequence. Specifically, the role of the knees changed to a movement pattern we would like to term "knee strategy" (Paper V).
- Alcohol intoxication at 0.06 and 0.10% BAC caused a complex multifaceted deterioration of human postural control, as reflected by differently changed body movement amplitudes of the upper and lower body segments. Particularly, the knees were used in a changed roll during the latter parts of the balance test. This finding suggests that a more complex multi-segmented movement pattern had to be used to manage the increasingly growing strain over time to handle balance perturbations whilst intoxicated (Paper VI).



# Populärvetenskaplig sammanfattning (Summary in Swedish)

Alkoholhaltiga drycker har konsumerats av människan sedan stenåldern. Det har antagligen varit känt att alkohol påverkar både balansförmåga och omdöme sedan förhistoriska tider och referenser till alkohol och berusning förekommer mycket tidigt i både historiska och religiösa texter. Dessa uråldriga observationer har under modern tid studerats under kontrollerat intag av alkohol. Man har observerat olika grader av både kognitiva och motoriska effekter av alkoholberusning. Det är emellertid mindre känt hur alkoholberusning i detalj påverkar balansen, vilka sinnen som påverkas, på vilket sätt sinnenas funktion förändras och varför man har en ökad fallrisk också vid lägre intoxikationsgrad.

Många studier av alkoholens effekter på balans är av äldre datum. Dessa studier har därför inte haft möjlighet att utnyttja nyutvecklade analysmetoder för att utvärdera alkoholkoncentration i blodet. De har inte heller haft möjlighet att använda nyutvecklade analysmetoder för att mäta och analysera människans balans, rörelsemönster och ögonmotorik, eller kunnat kombinera dessa mätningar med uppfattning av berusningsgrad. Alkohol förekommer emellertid också i sociala sammanhang i samhället. Det är därför av intresse att försöka undersöka och till del klarlägga om och hur alkohol i sådana koncentrationer kan förväntas påverka en icke missbrukande person. Av intresse är, påverkan på balans och orienterande ögonrörelser samt om dessa kan korreleras till uppfattning om berusningsgrad, vilket skulle kunna varna den påverkade individen.

För att studera alkoholens effekter på balansen undersöktes 25 friska försökspersoner när de var nyktra samt vid 0,6 och 1,0 promille. Alkoholhalten i blodet mättes noggrant var 15:e minut genom att analysera försökspersonernas utandningsluft. Balansen utvärderades genom att försökspersonen stod på en balansplatta som mätte krafterna från fötterna mot underlaget (posturografi). Kroppsrörelser och balans studerades också med hjälp av ett 3D-rörelsesystem (Zebris) där detektorer mätte de individuella rörelserna av huvudet, axlar, höfter, knän och anklar. Fötternas berörings- och vibrationskänsl utvärderades före alkoholberusningen och jämfördes sedan med balansresultaten. Innerörats balansorgan som känner av huvudrörelser och orientering analyserades av hur väl man kunde ställa in en linje i horisontal- och vertikalplanet i ett mörkt rum. Under ett test lades en snedvriden kvadrat till runt linjerna för att se om en visuell

störning påverkade personernas rumsorientering. Ögonrörelser analyserades med elektronystagmografi (ENG) där man mäter hur väl ögonen med hjälp av sackader (att flytta blicken mellan två punkter) och följerörelser (att stadigt följa ett rörligt objekt med blicken) kan följa visuella objekt som rör sig enligt förutbestämda mönster.

Balansen påverkades markant av alkohol och försämringen var ickelinjär under stigande alkoholdos. Balansen påverkas proportionellt mer av alkohol i sidled än i framåt- bakåttled.

Den annars naturliga förmågan att lära sig hantera balansstörningar bättre efter träning (adaption) försämrades eller försvann helt. Synen kunde förbättra balansen, speciellt i framåt- bakåttled, men gav sämre bidrag till stabiliteten vid berusning.

Känselsinnet i fötterna och förmågan att omvikta till känselsinnet är viktigt för balansen vid alkoholberusning. Ju bättre vibrationssinne i fotsulorna försökspersonerna hade desto bättre balans hade de med slutna ögon, speciellt vid 1 promilles alkoholpåverkan och under de senare delarna av balanstestet. Orienteringen i rummet, representerat av linjeinställningarna, påverkades mer av den omgivande kvadraten i berusat tillstånd jämfört med i nyktert. Detta kan tolkas som att man förlitar sig mer på synintryck i berusat tillstånd.

Redan vid 0.6 promille försämrades ögonföljerörelsernas förmåga markant att stabilt följa ett rörligt föremål under längre tid och sackadernas maxhastighet blev lägre. Vid 1.0 promille försämrades också följerörelsernas förmåga att nå upp till rätt följerörelsehastighet och sackadernas hastighet minskade ytterligare. Försökspersonernas subjektiva skattning av hur berusade de var överensstämde signifikant med hur stabilt man med ögats följerörelser kunde följa ett rörligt objekt.

Kroppens rörelsemönster förändrades av alkohol främst i slutet av balanstesterna med slutna ögon vid 1 promille. Personerna började då ta mer hjälp av knärorelser för att öka stabiliteten. I nyktert tillstånd klarar man normalt av att stabilisera kroppen framför allt med rörelser som utgår från anklarna och fötterna. Kroppsrörelsernas storlek och effektiviteten av synen att stabilisera kroppen var direkt kopplat till alkoholnivån i blodet. Den subjektiva upplevelsen av berusning stämde väl med hur stora kroppsrörelserna var i överkroppen.

Dessa resultat kan ge förklaringar till varför balansen är sämre under alkoholpåverkan och hur detta kan leda till fall och medföljande skador.

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# Appendix 1: Publications

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