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University of Bern

MEASUREMENT AND ANALYSIS OF EYE-HEAD COORDINATION IN PATIENTS WITH SCHIZOPHRENIA

PhD Thesis submitted by

SIMON GABRIEL SCHWAB

from **Kallnach BE, Switzerland**

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Thesis advisor
PD Dr. Andreas Altorfer
Department of Psychiatric Neurophysology
Medical Faculty of the University of Bern

Thesis co-advisor
Prof. Dr. René M. Müri
Department of Clinical Research
Medical Faculty of the University of Bern

Accepted by the Faculty of Medicine and the Faculty of Human Sciences of the University of Bern

Bern, 30. 1. 2014 Dean of the Faculty of Medicine

Bern, 10.2.14 Dean of the Faculty of Human Sciences

Contents

Abstract

Oculomotor deficits are well established in schizophrenia research. For example, there is large evidence that patients with schizophrenia exhibit specific differences in eye movement behavior in view of scanpath characteristics, number of fixations, antisaccade tasks and smooth-pursuit tasks. Looking at eye movements in neurological and psychiatric diseases involves a long and productive history in oculomotor research, reflecting two primary paths of scientific investigation (McDowell, Clementz, & Sweeney, 2011). First, establish valid markers that could identify the risk for developing such diseases. Second, identify the underlying psychophysiological substrates of such severe psychiatric conditions. While an impressive number of research papers established and confirmed consistent abnormalities, most prominently in smooth-pursuit and antisaccade tasks, abnormalities in eye-head coordination remain unclear. This seems surprising because eye movements are closely coupled with head movements in almost all situations in life, such as in social interactions and sports, even in reading eye movements are accompanied with minimal head movements. In real life situations, gaze shifts involve combined eye and head movements, extending the overall oculomotor range to perceive and interact with the surrounding world.

Thus, the present thesis aimed to develop the methodology to investigate eye-head movements in order to investigate potential aberrant patterns in eye and head movements within patients with schizophrenia. As a result of this thesis, three research papers are presented here. The first paper is a methodological work discussing the capabilities and limits of the eye-head tracking system used in comparison with other technologies. This work presents a behavioral task in which color squares and Landolt rings were presented in the periphery of the visual field to invoke eye-head shifts in that direction. A method to reconstruct signal loss in video-based oculography caused by cornea reflection artifacts is introduced in order to extend the tracking range of the system. Parameters of eye-head coordination are identified using EHCA (eye-head coordination analyzer), a MATLAB software which was developed for this thesis to analyze eye-head shifts. To demonstrate the capabilities of the approach, a study with 11 healthy subjects was performed to investigate motor behavior.

In the second research paper, a patient study is presented, showing that patients with schizophrenia exhibit a different saccadic-latency pattern compared to controls. Patients performed more head movements, and had increased eye-head offsets during combined eye-head shifts than controls. We concluded, patients with schizophrenia may not be able to adapt to the two different tasks to the same extent as controls. This can be interpreted as a specific oculomotoric attentional dysfunction and may support the hypothesis that schizophrenia patients have difficulties determining the relevance of stimuli. Patients may also show an uneconomic over-performance of head-movements, which is possibly caused by alterations in frontal executive

functions that impair the inhibition of head shifts. In addition, a model was created explaining 93% of the variance of the response times as a function of eye and head amplitude, which was only observed in the controls, indicating abnormal eye-head coordination in patients with schizophrenia. To conclude, the major contributions presented in this thesis were the development of the methodology to investigate eye-head coordination, and the patient study providing new evidence for abnormal eye-head coordination in schizophrenia. This thesis may open new perspectives, such as further research in evaluating eye-head coordination as potential marker for schizophrenia, or longitudinal studies linking eye-head coordination with psychopathology.

The third paper involves a collaboration beyond the topic of this thesis. I conducted the data analysis for a project that investigated physiological changes during the perception of music.

Chapter 1

Introduction

Important human brain functions involve emotions, thought and cognition, language and sensory perception, and therefore are major areas of research in cognitive neurosciences and psychology. However, another major component is *movement*. Movement is not only important to go from one place to another. Instead, without movement, it is not possible to express feelings and gestures, or to speak and communicate. Also, we cannot visually perceive the world without the movements of the eye. In Wolpert's (2011) line of argumentation, movement is one of the core functions that the brain was designed for, or the brains of species in general were designed for. Almost all aspects of our lives involves some type of movement, e.g., movement of limbs and fingers, movements of inner organs such as lungs and heart, or movement of facial muscles and the tongue. Even in relatively passive situations, such as reading (Rayner, 1998) or watching television (Tseng et al., 2013), we extensively move our eyes in order to perceive, not only the real world, but also during sleep and imagery (Brandt & Stark, 1997). Eye movements are triggered by six eye muscles working in pairs connected by three cranial nerves receiving input from a number of brain regions, some low-level subcortical regions, but also higher-level regions in the cortex. This accounts for the fact that eye movements can be triggered by bottom-up processes, such as by a change of an object, for example a car suddenly appears in one's field of vision, or by top-down processes, such as a gaze shift towards a familiar face. An approach to investigate of eye movements, is modeling eye movements in computers. Such models have to account for both higher cortical functions such as attention but also data-driven methods such as image analysis in order to make predictions of natural, behavioral eye movements (Itti & Koch, 2001), but this process is complex and even though much is known about human perception, there are still many questions to be addressed in research. In conclusion, movement and visual perception, are major brain functions that are highly relevant in every day life.

Movement and perception are major brain functions

Eye movements are strongly related to the anatomy of the eye: The fovea, a single spot on the retina has the highest density of photoreceptors forming the position of highest resolution and sharpest vision. Therefore, we constantly move our eyes to perceive a sharp surrounding world, while at the same time, objects in the periphery of the visual filed always remain unclear. Head movements are used in addition to extend the oculomotor range. During eye movements, the eye performs jumps (saccades) to attend new objects of interest and short stops (fixations). Only during fixations the sensory input is fully processed in order to perceive the surrounding scene (Bridgeman, Hendry, & Stark, 1975). Even during a fixation, the eye never rests completely and

Fixations and saccades

performs minimal movements (fixational eye movements) in order to prevent neural adaption leading to perceptual fading of the scene (Martinez-Conde, Otero-Millan, & Macknik, 2013).

Studying eye-head coordination

The fact that movement is a major brain function becomes even clearer considering a large number of neurological and psychiatric conditions that can affect movement: Parkinson's disease, multiple sclerosis, head injury, stroke, schizophrenia, depression, Alzheimer's disease, Tourette syndrome and more. These diseases can all affect the motor system showing its resulting malfunction. At the other end of the spectrum, for example in sports, the human motor behavior remains a complex high-performance machinery, which becomes obvious in very challenging task such as hitting and catching a ball in baseball or cricket (McBeath, Shaffer, & Kaiser, 1995; Land & McLeod, 2000). In such tasks, predominately the motor system combined with the visual system have to perfectly perform complex tasks within hundreds of milliseconds. For example "at bat", the batter's eyes precisely follow the ball during its trajectory, a swing is performed that hits the ball at the sweet spot, all within less than 500 ms. Here, the visual, oculomotor and motor system are highly challenged, and diseases such as schizophrenia can affect such motor and attentional tasks. Therefore, the present thesis investigates eye-head coordination in patients with schizophrenia. To this aim, two separate studies were conducted and presented as research articles in Chapter 2 in order to find potential differences in eye-head coordination between patients with schizophrenia and healthy controls. Both studies involved an experiment in which different types of visual targets were presented to investigate effects on behavior in terms of oculomotor and motor performance in patients with schizophrenia compared to healthy controls.

Overview of the chapters

The thesis is structured in four chapters. Chapter 1 provides a general overview of the main topic of the present thesis: schizophrenia, the physiology of eye movements and the methods of eye tracking and eye-head tracking in particular. The main part of this thesis is Chapter 2: here, empirical research is presented in the form of three original research articles in peer-reviewed journals. The first work has been published in the *Journal of Eye Movement Research* on the topic of measurement and analysis of eye-head coordination, forming the foundation for the second work. The second work involves a paper published in *PLoS ONE* about abnormal eye-head coordination in patients with schizophrenia. In addition I have conducted the data analysis in a study which investigated physiological changes during the perception of classical music published in *Psychophysiology*. Due to its different topic, this paper and my contributions are only briefly discussed in Chapter 3, which focuses as overall discussion on the first two research articles. To conclude, future perspectives are provided in the last part of the thesis (Chapter 4).

1.1 Schizophrenia

Symptoms and prevalence

Schizophrenia is a serious psychiatric condition involving a variety of symptoms, such as delusions (wrong beliefs), hallucinations (e.g., hearing voices), loose associations, flat emotions, and motor symptoms (for an overview van Os & Kapur, 2009). Schizophrenia typically has an onset in young adulthood and starts less frequent in childhood or adolescence (Clemmensen, Vernal, & Steinhausen, 2012). The global lifetime prevalence is 4 per 1'000 persons, and there seem to be no difference in occurrence between males and females, between urban and rural areas, and across epochs, however, developed countries may have more occurrences than less-developed countries (McGrath, Saha, Chant, & Welham, 2008).

Diagnosis

From a historical point of view (First, 2009), Emil Kraeplin (1856–1926) was among the first who observed a common pattern of hallucinations and bizarre delusions in these patients. Eugen Bleuer (1857–1937), a swiss psychiatrist, introduced the term *schizophrenia*, which mean 'split brain'. Bleuer's description of schizophrenia accounted for a much more heterogeneous disease, compared to Kraeplin, containing primary symptoms (profound ambivalence, looseness of associations, disturbance of affect and living in an internal, unrealistic word) and secondary symptoms (hallucinations and delusions). Nowadays, diagnosis according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) incorporates at least two or more of the following symptoms, each present during a 1-month period: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, (5) negative symptoms (i.e. affective flattening, alogia or avolition). The DSM, but also the ICD (International Classification of Diseases), define schizophrenia as a categorical diagnosis, that is, a particular individual tested either has, or has not schizophrenia according to this definition. However, patients with schizophrenia may sometimes experience very different symptoms and severity which may be better understood on a continuous symptom scale instead of in discrete categories. A widely used instrument in clinic and research is the 'Positive and Negative Syndrome Scale' (PANSS; Kay, Fiszbein, & Opler, 1987), assessing the severity of a variety of symptoms, summing up the items in a positive and negative symptoms score. While positive symptoms refer to an abnormal presence of a specific behavior or state, such as hearing voices, negative symptoms refer to a specific lack, such as flat emotions. Even though such a dichotomous view improved the understanding and treatment of schizophrenia, factor analytic studies propose that schizophrenia is organized into three symptom domains: psychotic symptoms (hallucinations and delusions), disorganization symptoms (thought disorders, bizarre behavior, inappropriate affect), and negative symptoms (Grube, Bilder, & Goldman, 1998). Other scales assesses language, affect and motor behavior in order to understand symptoms in relation to major brain system such as the language, limbic and motor system (Strik et al., 2010). This approach allows to link psychopathological assessment to brain activity in neurophysiology and brain imaging studies.

Motor symptoms

The occurrence of motor symptoms is surprisingly high in schizophrenia with a prevalence rate of 12–97% in first-episode, medication-free patients (Walther & Strik, 2012). Most common are neurological soft signs, dyskinesia, parkinsonims and catatonic symptoms, see Table 1.1 for a description. However, some problems have to be addressed: first, motor symptoms can also be caused by psychopharmacological treatments, and with the rise of medical treatment in the last decades, attention has shifted towards these effects. Clinical distinction between drug-induced symptoms and disease-specific symptoms are difficult to establish. Thus, treatment with antipsychotic medication is a major limitation of the literature on the motor dysfunction in schizophrenia. Second, there is conceptual overlap, such that motor signs can be assigned to multiple categories. Third, such motor symptoms are not only present in schizophrenia but may also occur in neurological or other psychiatric conditions, for example major depression (Razavi et al., 2011). Today, studies using magnetic resonance imaging (MRI) investigate potential association between symptom severity and impaired brain function and structure by techniques such as functional magnetic resonance imaging (fMRI), arterial spin labeling (ASL; Horn et al., 2009) and diffusion-tensor imaging (DTI; Bracht et al., 2013, 2012; Walther et al., 2011).

Conclusion

As a concluding remark, classification systems such as the DSM definition of schizophre-

Table 1.1: Motor symptoms in schizophrenia (adapted from Walther & Strik, 2012).

Type	Description
Neurological soft signs	Abnormalities in coordination, sensory integration and sequential motor acts, for example: gait, balance
Dyskinesia	Abnormal, involuntary movements, for example repetitive movements of the head, mouth, face, limb, trunk, respiratory musculature
Parkinsonims	Resting tremor, rigidity, bradykinesia, loss of postural reflexes, flexed posture, motor blocking
Catatonic symptoms	Mutism, posturing, mannerisms, immobility, rigor, stereotypes, catalepsy, grimacing, waxy flexibility
Psychomotor slowing	Reduced processing speed, reduced reaction times, for example present in fine motor task, drawing, and writing
Negative syndrome	Loss of affective experience and expression, decreases spontaneous movements and reduced activity

nia disorder, even though popular in daily clinical practice, may lack to provide meaningful information to patients and clinicians in view of subtypes, long-term prognosis and predictability of treatment outcome. Here, research in psychophysiology, brain imaging, genetics and neurobiological studies may become more important in the future to provide such information.

1.2 Physiology of Eye Movements

The nature of eye movements

The visual impression we have from the world is constructed by our brain's visual system, for example colors and contrast. Visible light, a small portion of a wide electromagnetic energy spectrum surrounding us, is transferred into vivid pictures and impressions, transmitted by the light-sensitive photoreceptors of the eyes. These photoreceptors are highly specialized nerve cells forming a light-sensitive tissue in the inner of the eye, the retina (the retina has an equivalent function as the light-sensitive film of a photo camera). However, these sensory nerve cells are not equally distributed on the retina. Instead, only a single spot contains the highest density of photoreceptors: the fovea. The fovea provides the required spatial resolution to perceive a sharp, detailed image. Eye movements can direct the fovea to objects, faces or other areas of interest within the visual field, a process called foveation. Therefore, the underlying nature of eye movements is closely connected to the anatomy of the eye, or the architecture of the retina, respectively. Eye movements are important to perceive the visual scenery of the world surrounding us. In humans, the eyes constantly move to scan the visual environment.

Extraocular muscles

During eye movements, the eye performs successive jumps and stops, called saccades and fixations. A fixation usually lasts for 100 ms or longer, during this period, visual information is processed from the retina to the visual system in the brain. A saccade lasts for a few tens of milliseconds, depending on its size, and little or no visual perception occurs in that time (Bremmer, Kubischik, Hoffmann, & Krekelberg, 2009). Eye movements are controlled by 3 antagonistic pairs of muscles (extraocular muscles): the lateral and medial rectus muscles, the superior and inferior rectus muscles, and the superior and inferior oblique muscles. These muscle pairs can move the eye in 3 axes: horizontal, vertical and torsional. Horizontal movements are

Table 1.2: Innervation and action of the extraocular muscles.

Muscles	Cranial Nerve	Nucleus	Action
Rectus			
lateral	Abducens (IV)	Abducens (Ponds)	Abduction
medial	Oculomotor (III)	Oculomotor (Midbrain)	Adduction
superior	Oculomotor (III)	Oculomotor (Midbrain)	Elevation
inferior	Oculomotor (III)	Oculomotor (Midbrain)	Depression
Oblique			
superior	Trochlear (IV)	Trochlear (Midbrain)	Depression
inferior	Oculomotor (III)	Oculomotor (Midbrain)	Elevation

movements towards the nose (adduction) or away from the nose (abduction) and are entirely controlled by the medial or the lateral rectus muscles, respectively. Vertical movements, upwards (elevation) and downwards (depression), are controlled by the superior and inferior rectus muscles as well as by the oblique muscles (Purves et al., 2012, p. 436). For elevation, the superior rectus and the inferior oblique are used, for depression, the inferior rectus and the superior oblique are used. However, when the eye is abducted, the rectus muscles (inferior and superior) are the main vertical movers, when the eye is adduced, the oblique muscles are the main vertical movers. The extraocular muscles are innervated by 3 motor cranial nerves that connect to their originating subcortical nuclei: the abducens, the trochlear and the oculomotor nerve (Table 1.2). Beside the extraocular muscles, the oculomotor nerve also controls the levator muscles of the eyelid, the ciliary muscles to change the shape of the lense (accommodation reflex) and the ciliary muscles to constrict the pupil in bright light (pupillary reflex). The trochlear nerve, compared to the others, innervates its destination muscle on the contralateral side.

Types of eye movements

Some decades ago, Alfred Yarbus, a Russion physiologist, was among the first who investigated and measured eye movements (Tatler, Wade, Kwan, Findlay, & Velichkovsky, 2010). In his pioneering work, Yarbus displayed scanpaths during viewing of images. During viewing, successive fixation and saccades were performed, summing up to an overall scanpath revealing a fixational pattern on the images, indicating that distinct features such as the eyes, the nose and the mouth are the parts containing most of the fixations. During picture viewing, usually saccades are performed. However, these are not the only type of eye movements. There are five types of eye movements (Purves et al., 2012, p. 438). Three for gaze shifts: saccades, smooth pursuit movements, and vergence movements; and two for gate stabilization: the vestibulo-ocular and the optokinetic reflex. Their functions are described in Table 1.3.

Saccadic latency

Looking at a picture or landscape usually involves saccades as the major type of eye movements. Also in the experiments presented in Chapter 2, saccades are the main eye movements performed by the participants, although vestibulo-ocular reflexes may also occur because participants turn their head in these experiments. The primary goal of saccades is to change direction of gaze towards a new target of interest. However, there is a temporal lag preceding the initiation of the saccade which is used to resolve the two following tasks: the direction of the saccade and is amplitude is computed in order to hit the target, this is also known as ballistic process because no correction can be made if the target moves during the execution of the saccade. Instead, a second and smaller corrective saccade is conducted. The time to prepare the saccade, the saccadic

Table 1.3: Types of eye movements and their function.

Type	Control	Function
Gaze shift		
Saccades	Voluntary and reflexive	Change of gaze position
Pursuit	Voluntary	Tracking of moving objects
Vergence	Reflexive	Convergence: Align close and distant targets on the fovea
Gaze stabilization		
Vestibulo-ocular reflex	Reflexive	Compensate head movements
Optokinetic reflex	Reflexive	Combination of saccades and smooth pursuit to track large-scale movements

latency, last for about 200 ms, which could be replicated in our experiments (Schwab, Würmle, & Altorfer, 2012).

Neuronal control

Multiple brain areas are involved in the accurate targeting of the saccadic eye movement, most importantly the frontal eye field (FEF), the superior colliculus (SC), and the paramedian pontine reticular formation (PPRF). Here, we give a short summary on the neural control of saccadic eye movements described by Purves et al. (2012, p. 440–450):

The FEF and the SC both contain a topographical map of eye movement vectors. Thus, activation of a particular spot in the FEF or the SC cause a saccade of a specified direction and amplitude. The SC contains both a sensory map of the visual field and a motor map which both are in register, so that visual cells responding to a stimulus in a specific region are located directly above the motor cells that invoke motor commands to invoke saccades to this region in the visual field. However, this is a simplified model, the activation of neurons in the visual map is neither necessary nor sufficient to activate neurons in the motor map resulting in saccadic generation. These two layers in the SC are influenced and linked by cortical regions, for example the FEF. To illustrate just one example of a circuit, the FEF projects to the SC, which in turn projects to the PPRF. The PPRF connects to the abducens nucleus having connections to the oculomotor nucleus. As we have already seen, these two nuclei and their corresponding cranial nerves innervate the lateral and medial rectus. Thus, taking this circuit, activity in the FEF can trigger saccades in the horizontal axis in this example. Of course, this short illustration is far from a complete description of all the circuits involved in neural control of saccades or the other types of eye movements.

1.3 Eye-head coordination during gaze shifts

Experiments allowing eye-head shifts are more naturalistic

In many eye movement studies, the head remains fixed, and changes in eye movements directly reflect changes in gaze position. Thus, eye position can be directly related to gaze position in space. A major argument to study eye-head coordination is to more fully target the natural capabilities of the oculomotor system (Corneil, 2011). Targets appearing beyond $\pm 15°$ in the periphery usually comprise an eye-head shift (i.e., an eye saccade and a head shift) towards the target position, extending the oculomotor range (Proudlock & Gottlob, 2007). It has to be noted that in eye-head shifts the underlying neuronal circuits become more complex as both

systems have to be perfectly adjusted and timed to precisely land on the target. Such shifts require multiple motor system and can produce more flexible patterns of coordination. Also, ocular behavior become more diverse, for example allowing for eye movements without changing gaze position such as the vestibulo-ocular reflex. Further, eye-head shifts have large methodological implications, since the mapping from eye position to gaze-in-space position is not trivial. In conclusion, the main purpose of head movements in addition to eye movements are the extension of the range, and the stabilization of the retinal image (e.g., vestibulo-ocular reflex and optokinetic reflex). However, in addition, head movements also have the purpose of emotional expression and communicating properties, for example nodding.

Properties of eye-head shifts

During eye-head shifts (for a review Proudlock & Gottlob, 2007), a variety of behavioral patterns are possible, also dependent on the experimental task. However, there are some physiological constraints, which are now briefly reported. First, the head range is limited (Chen, Solinger, Poncet, & Lantz, 1999): 90° roll, 125° pitch (vertical) and 150° yaw (horizontal). The human visual field extends to approximately 60° nasal, 90° lateral, 60° upwards, and 75 ° downwards. Saccades can be up to 90° with a maximum speed of 750°/s. In eye-head shifts the saccade is initiated prior to the head shift in the experiments conducted, after a saccadic latency of approximately 200 ms in which the motor commands are programmed (direction and amplitude). Then, after 50-121 ms (Schwab et al., 2012) the head starts to turn in the same direction (head offset). When the saccade has reached the target, the eye performs a compensatory movement during fixation (vestibulo-ocular reflex) in the opposite direction, perfectly compensating the not yet completed head movement, allowing gaze stabilization. These two types of eye movements are of different nature (as previously discussed, see 1.3). While the former saccade is top-down and has a larger speed and amplitude, the later compensatory movement is reflexive, slower in speed (i.e. same speed as the head movement) and usually of smaller amplitude. However, different patterns may occur, for example the head movement starts prior to the eye, depending on the experimental tasks used.

1.4 Overview of abnormal eye movements in schizophrenia

Many studies report abnormal eye movements in schizophrenia in different types of experimental paradigms, most often: Antisaccade task, natural viewing and smooth pursuit. Table 1.4 provides a literature overview of oculomotor findings in schizophrenia for these paradigms.

Antisaccade task

In anti-saccade tasks (for a review, see Munoz & Everling, 2004), a fixation point is presented and after a moment, a second appears at another position. Subjects require to make a saccade in the opposite direction away from the second fixation point, rather than towards it. This task is suitable to investigate the voluntary control of eye movements. In schizophrenia, two major finding are prominent in the antisaccade tasks: prolonged reaction times and increased error rates by conducting a saccade toward the second fixation point. Since the second fixation point can trigger a bottom-up pro-saccade, this process needs to be actively suppressed top-down in order to perform a saccade towards the opposite direction. A candidate structure to be impaired in schizophrenia is the dorsolateral prefrontal cortex (DLPFC). Impairments of the DLPFC in schizophrenia can account for these specific findings in the antisaccade task (Munoz & Everling, 2004), for example, patients with DLPFC lesions show reduced performance in antisaccade task

Table 1.4: Overview of findings in patients with schizophrenia.

Type of paradigm	Abnormality	References
Antisaccade task	Higher error rates, longer antisaccade latency	Calkins, Iacono, and Curtis (2003, F), Campanella and Guerit (2009), Crawford et al. (1998, F), Ettinger et al. (2005), Fukushima et al. (1988), Fukushima, Fukushima, Morita, and Yamashita (1990), Hutton and Ettinger (2006), Kallimani et al. (2009), Kang, Dionisio, and Sponheim (2011), Levy et al. (2008), Light et al. (2012), Mazhari et al. (2011), Nieman et al. (2007, R), Nkam et al. (2001), O'Driscoll, Lenzenweger, and Holzman (1998), Petrovsky et al. (2009), Reilly, Harris, Khine, Keshavan, and Sweeney (2008), Reuter, Rakusan, and Kathmanna (2005), Thaker et al. (2000, F), Zanelli et al. (2009, F)
Natural viewing	Reduced scanpaths, fewer number of fixations, neglecting salient visual features	Beedie, Benson, and St Clair (2011), Beedie, Benson, Giegling, Rujescu, and St Clair (2012), Egaña et al. (2013), Green, Williams, and Davidson (2003), Green, Waldron, Simpson, and Coltheart (2008), Loughland, Williams, and Gordon (2002b), Loughland, Williams, and Gordon (2002a), Loughland, Williams, and Harris (2004, F), Manor et al. (1999), Minassian, Granholm, Verney, and Perry (2005), Nishiura, Morita, Kurakake, Igimi, and Maeda (2007), Suzuki et al. (2009), Takahashi et al. (2008, F), Tonoya, Matsui, Kurachi, Kurokawa, and Sumiyoshi (2002), Williams, Loughland, Gordon, and Davidson (1999)
Smooth pursuit	Corrective saccades (back-up, catch-up), reduced gain	Beedie et al. (2012), Benson et al. (2012), Calkins et al. (2003), Ivleva et al. (2013), Kallimani et al. (2009), Lencer et al. (2008), Lenzenweger and O'Driscoll (2006, S), Nagel, Sprenger, Steinlechner, Binkofski, and Lencer (2012), Nkam et al. (2001), Nkam et al. (2010), O'Driscoll et al. (1998), Ross et al. (2002, F), Schwartz, O'Brien, Evans, Sautter, and Winstead (1995), Siever, Coursey, Alterman, Buchsbaum, and Murphy (1984, S), Siever et al. (1994, S), Smyrnis et al. (2007, S), Smyrnis et al. (2011), Spering, Dias, Sanchez, Schütz, and Javitt (2013), van Tricht et al. (2010, R)
Eye-head coordination	longer saccade and head latency, longer eye-head offset, more head movements	Fukushima et al. (1990), Schwab, Würmle, Razavi, Müri, and Altorfer (2013)

F: Studies involving first-degree relatives of patients with schizophrenia. R: Studies involving subjects at high-risk for developing psychosis. S: Studies involving groups with schizotypal personality.

similar to patients with schizophrenia.

In natural viewing, often scanpaths and fixations are investigated while subjects looked at natural scenes such as landscapes, faces or abstract geometric figures. Patients with schizophrenia often show reduced spatial scanpaths and fewer fixation, an indication for a reduced processing of the overall image information. This finding is proposed as potential diagnostic instrument (Benson et al., 2012; Suzuki et al., 2009). Natural viewing

During smooth pursuit, the eye follows a moving target and provides a stable image on the retina. Patients with schizophrenia exhibit reduced gain (inability to match pursuit velocity to target velocity) and more corrective saccades. Such findings may be caused by altered motion processing brain areas, for example V5 (Nagel et al., 2012). Smooth pursuit

In sum, consistent finding in three major paradigms provide evidence for abnormal eye movements in schizophrenia. These abnormalities are also found in ultra high-risk groups, schizotypal personality, and first-degree relatives, and therefore discussed as potential endophenotype or biomarker for schizophrenia. However, only few studies investigated eye-head coordination in schizophrenia which is aimed by this thesis.

1.5 Methods

The most commonly used eye-tracking systems record eye movements with a high-speed video camera (up to 200 Hz, sometimes up to 1000 Hz), known as video-oculography (for an overview Duchowski, 2007). The eye trackers are equipped with proprietary software to record eye movements and save eye position and point of regard to data files. Eye position is determined by calculating the centroid of the pupil from the image. However, usually real-world position is of interest (point of regard, or gaze). Therefore, eye positions are mapped to real-world coordinated, which requires a calibration step at the beginning of the experiment. During calibration, subjects fixate a number presented real-world points, and eye position is recorded. Now, eye-positions can be related to real-world points using a linear function, and all intermediate point are interpolated. Usually, the first cornea reflexion is also recorded to improve overall precision. Finally, the gaze positions can be exported to ASCII files for further processing. Eye tracking

In order to study eye-head coordination, additional hardware and software is required. We used a combined eye (iView X HED-MHT, SMI, Germany) and head (Fastrack, Polhemus, USA) tracking system. Gaze position, pupil position and head position were recorded (200 Hz) and saved to ASCII files using iView X (SMI, Germany). However, raw data from eye and head position have to be transformed to a higher level for meaningful data interpretation. In this thesis, the software to conduct an eye-head coordination study, and also the analysis software were developed and released with an open-source license on one of the major free software development platforms: SourceForge. Different hardware systems to measure eye-head coordination, which usually consist of an eye tracker connected to a motion tracking system, are compared and discussed in Chapter 2.1 (Schwab et al., 2012). Here, the software is shortly introduced that was developed during the thesis, including some summary statistics in Table 1.5. Eye-head tracking

PVRT (Peripheral Visual Recognition Task, Schwab, 2010) is a software to study the physiology of eye-head coordination. The study of eye-head coordination requires a paradigm that invokes both eye and head movements. Therefore, with this software, visual targets are Experiment software

Table 1.5: Software packages to study and analyze eye-head coordination.

Package	No. of classes	No. of methods	Lines of Code	Licence	Platform	Language
PVRT: Peripheral visual recognition task	16	82	1757	GPL 3	Linux	Python
EHCA: Eye-head coordination analyzer	6	38	1064	GPL 3	Win, Mac, Linux	MATLAB

presented in the periphery of the visual field. In the lab, these targets are reflected by mirrors to be drawn on two lateral stimuli screens (left and right of the subject). The software is written in the Python Programming Language using the PsychoPy Framework (Peirce, 2008, 2007). Some of the features of the software are: presentation of visual stimuli using OpenGL, Landolt Rings taken from a standardized letter chart (Pelli, Robson, & Wilkins, 1988), recording of subject responses through parallel port using the PortIO library (Stewart, 2006), eye and head calibration, notification of the eye tracker (TTL signals) for time synchronization, and export to raw data files for further processing (e.g., in MATLAB).

Analysis software

EHCA (Eye-Head Coordination Analyzer, Schwab, 2011) is a MATLAB application to analyze eye-head coordination. Eye/head tracking data and experiment data (PVRT) is synchronized and processed, some main features steps are: data segmentation and plotting of each experimental trial, data interpolation and filtering, and eye and head movement analysis (e.g., saccade latency, eye-head offset time, saccade amplitude and duration, head amplitude and duration).

1.6 Objectives

Developing the methods

The thesis investigated eye-head coordination abnormalities in patients with schizophrenia. In order to conduct an eye-head coordination study, the required methodology and software had to be developed first. During pilot studies, an experiment was created including a paradigm to invoke eye-head shifts with a level of difficulty suitable for both a control group and patients of schizophrenia. An apparatus had to be constructed to present visual targets in the periphery of the visual field. A critical aspect was also the development of software, especially analysis software. Most commercial analysis software of popular eye-tracking systems are limited to the classification of data point to fixations or saccades. Even though such an analysis may be suitable for ordinary eye-tracking experiments, for example in simple picture viewing, eye-head coordination analysis has other requirements. Such data also include head data that has to be addressed and taken in relation to eye movement data. Also, during eye-head shifts multiple ocular behavioral patterns occur to be considered, not only fixations and saccade, also compensatory eye movements. Thus, the thesis consists of a methodological work, forming the basis for the patient study.

Patient study

In the successive patient study, a sample of patients with schizophrenia and healthy controls (each n=14) was investigated in an eye-head coordination paradigm. We hypothesized that patients exhibit a different eye-head coordination pattern, e.g. saccade latencies, number of head shifts, compared to controls. We were also interested in to what extend eye-head coordination

behavior is dependent on the two different tasks presented (an easy color task, and a more difficult Landolt C orientation task).

Chapter 2

Results

2.1 Analysis of eye and head coordination in a visual peripheral recognition task

Schwab, S., Würmle, O., & Altorfer, A. (2012). Analysis of eye and head coordination in a visual peripheral recognition task. *Journal of Eye Movement Research, 5*(2), 1–9. http://www.jemr.org/online/5/2/3

2.2 Eye-head coordination abnormalities in schizophrenia

Schwab, S., Würmle, O., Razavi, N., Müri, R.M., & Altorfer, A. (2013). Eye-head coordination abnormalities in schizophrenia. *PLoS ONE, 8*(9):e74845. doi:10.1371/journal.pone.0074845

2.3 Music, perceived arousal, and intensity: Psychophysiological reactions to Chopin's "Tristesse"

Mikutta, C. A., **Schwab, S.**, Niederhauser, S., Würmle, O., Strik, W., & Altorfer, A. (2013). Music, perceived arousal, and intensity: Psychophysiological reactions to Chopin's "Tristesse". *Psychophysiology, 50*(9), 909–919. doi:10.1111/psyp.12071

Chapter 3

Overall Discussion

The main objective of the thesis was to investigate eye-head coordination in patients with schizophrenia. In the scientific literature, consistent oculomotor deficits were found in schizophrenia, most prominently problems in antisaccade and smooth pursuit tasks. This thesis provides new evidence for abnormal eye-head coordination in schizophrenia. During every-day tasks such basic visuomotor tasks are performed a number of times, revealing problems at an already early stage of visual processing. Also the relatively simple task we used, such as recognition of symbols and colors, seem to be sufficient to find behavioral and oculomotor differences. However, it might be interesting to use more complex stimuli, for example emotional faces that can further enlarge oculomotor differences between patients and healthy controls (Loughland et al., 2002a, 2002b). The findings suggest that such perceptual alterations contribute to cognitive dysfunctions in schizophrenia (Butler & Javitt, 2005). One can speculate that non-optimal visuomotor behavior can further enlarge misconceptions and abnormal thoughts when objects are not optimally attended to.

CR reconstruction

One of the methodological challenges in this thesis was the signal loss of the cornea reflection (CR). Usually, video-based eye tracker record both the pupil and the CR which is superior compared to pupil-only tracking in view of spatial precision. Since in eye-head coordination paradigms large saccades are performed, the signal from the CR can disappear resulting in a complete loss of data. Therefore, we developed a method to reconstruct the gaze signal from the pupil data. Upon these two signals (incomplete gaze signal and robust pupil signal), a fit is performed, and its coefficients are used to create the new reconstructed signal (see Chapter 2.1, Figure 2b). This approach not only allows to be used in eye-head coordination studies but also applies to all video-based eye tracking that suffer from CR loss. However, if target displacement is in the far eccentricity (as in our paradigm, or generally in eye-head coordination studies) then such artifacts may occur more frequently, and in this case, our approach is most notably helpful.

VOG vs. EOG

In a comment by a reviewer, another recording method called electrooculography (EOG) has been suggested by the statement that it remains at present the best solution for eye-head coordination studies, if we reject magnetic search coil due to the level of discomfort for the subject. For example, recent studies still use EOG (e.g., Becker et al., 2009). However, it is difficult to generally suggest one method as superior over the others, since all the tracking methods have their advantages and disadvantages. For example, EOG suffers from drifts and larger noise. Therefore, we provided a table with an overview of the most popular oculomotor

tracking methods (see Chapter 2.1, Table 1). Nowadays, VOG is the most popular tracking method, and there are recent eye-head coordination studies using VOG (e.g., Richard, Churan, Guitton, & Pack, 2011). Whatever tracking method is used, it is cruel to identify the weaknesses of the system in use, and to address these problems in order to achieve satisfactory data quality. The challenge using VOG in eye-head coordination studies it clearly the CR artifacts, and this thesis provides a solution to remove such artifacts.

Tracking range

Another issue, which is related to the previous one is the tracking range. Horizontal tracking range in VOG is typically up to $\pm 40°$ (Holmqvist et al., 2011), exact tacking ranges may differ from subject to subject. Other methods, such as scleral coil and EOG do not have any limit concerning tracking range. However, these methods suffer from other disadvantages, for example heavy discomfort for the subjects or drift and noise in the data. In VOG, during very large saccades, the CR signal is more vulnerable that the pupil signal and can disappear when the glint is leaving the iris and merges with the sclera at large eye rotations, becoming indistinguishable, or, when the CR is covered by eyelashes or eyelids. The techniques to reconstruct CR artifacts proposed in this thesis address these problems and extend the tracking range. For further experiments, to limit the amount of reconstruction and other data improving techniques during preprocessing, the targets can be positioned at a smaller eccentricity of $\pm 40°$ instead of $\pm 55°$ used in the experiments presented here.

Visual paradigm

A visual paradigm was developed in this thesis: the peripheral visual detection task. This paradigm has been criticized in two ways. On the one hand, it was commented that the paradigm was to complex compared to simple LED diodes used in the classical studies. Presenting LEDs and ask the subjects to look at the targets may be the standard procedure and is very suitable to investigate the basics of eye-head coordination, which has been done multiple times. However, there are also studies who use more sophisticated protocols to study eye-head coordination, for example, by using different sensory modality as auditory vs. visual (Goossens & Van Opstal, 1997) or different instructions, for example simply look at the target vs. target identification (Guyader, Malsert, & Marendaz, 2010). Using such protocols, it is possible to study the effect of specific task manipulation on eye-head coordination. We created a visual recognition task to get additional behavioral measures such as response accuracy and reaction times. A recognition task is a popular standard task in psychological sciences, but has rarely been applied in eye-head coordination studies. This task requires resources in visual short term memory and attention in combination with gaze control. Such a protocol is highly suitable to investigate in schizophrenia, which involves attentional and motor symptoms.

On the other hand, it was objected that the task was too simple with respect to the overall large number of correct responses. The tasks are not extremely cognitively challenging because overall correct responses were above 90%. However, task difficulty was nevertheless well chosen because of two reasons: first, a large number of correct responses was absolutely desired, since only correct responses were analyzed. Calculating statistics from mixed parameters of correct and incorrect responses may potentially confound the results. Increased task difficulty with only half of the trials correctly answered, involves less trials to be available for analysis. In sum, we were interested in the observation of eye-head movement patterns when the trial were answered correctly.

Second, the correct response rate revealed a drop in performance in the patient group during

the Landolt task. The performance was still slightly above 90%, but it is nevertheless a significant drop in performance revealing meaningful performance issues in the patient group in such a relatively simple task. Last but not least, concerning the response time, it is important to note that our task paradigm perfectly differentiated subjects according to task and group (e.g., controls in the color task had the shortest, patients in the Landolt task had the largest response times). This means, response time is largely dependent of both what group and what task a subject belongs to.

Collaboration

In addition I would like to address a different project which was my main collaboration during my PhD project. This study investigated physiological changes during music perception (Mikutta et al., 2013). Twenty amateur musicians participated in the study. Their subjective arousal and objective measures such as heart rate were investigated in relation to two different interpretation of Chopin's "Tristesse": One version with more rhythmic tension, one with less. We found that perceived arousal strongly correlated with sound intensity (loudness). Heart rate showed only little response to changes in sound intensity. Larger changes in heart rate were caused by a version with more rhythmic tension. Therefore, we conclude that autonomous nervous activity cannot only be modulated by intensity but also by more subtitle rhythmic changes. However, correlating the time series of different signals may be challenging. The compared signals may be correlated with one another at different frequencies or time points. My contribution to this study was the applications of semblance analysis, originally developed from geosciences (Cooper & Cowan, 2008), to the physiological data set of this study. Two signals can be analyzed as a function of both scale (or wavelength) and time. In such semblance plots, it is possible to compare the different time segments and frequency domains of the two signals. Although this study was not related to eye-head coordination, another study conducted eye tracking during music performance: They investigated eye movements in violin players showing that musical performance can be investigated using this method (Wurtz, Mueri, & Wiesendanger, 2009). They found that the eye-hand span (the time between reading the score and acting) is not only influenced by expertise but also by the complexity of the score to be played. It may be interesting to investigate the both the physiological reactions and eye movements during professional music performance of high-skilled players.

Scientific contribution

The main result of the present thesis is the different saccadic latencies which is modulated by the type of task presented and which could be observed in the control group but not in the patient group. Also another main result is the modeling of the response time using the eye-head coordination pattern explaining a very large amount of variance (93%) of the data in the control group but not in the patient group indicating abnormal eye-head coordination patterns in the patient group. In an aging study, also using model building, eye-head coordination and sedative use successful predicted 1-year history of falls in elderly woman (Di Fabio, Greany, Emasithi, & Wyman, 2002). In general, creating models from data can be very powerful since it takes multiple variables into account and evaluates each of them for its relevance. Finally, models cannot only be tested for significance but also compared to other models.

Part of this thesis replicated findings from Kolada and Pitman (1983), who observed an excess of head movements in patients with schizophrenia. However, they did not quantify saccade latencies and eye-head coordination (e.g., eye-head offsets) in the same extend. To our knowledge, the study by Fukushima et al. (1990) is the only work who quantified eye-head coordination in patients with schizophrenia. Even though in this work 32 patients and 36 controls were involved,

they examined eye-head coordination in a saccade and antisaccade task in 5 patient and 5 controls only. Therefore, we believe that our study contributes to this field in providing new findings in patients with schizophrenia (Schwab et al., 2013), replicating previous findings, and providing the methods to analyze eye-head coordination (Schwab et al., 2012). Also, this work succeeds to investigate motor and attentional symptoms in an objective and concept-free manner as requested in a recent review on motor symptoms in schizophrenia (Walther & Strik, 2012).

Chapter 4

Perspectives

The research presented here provided evidence of abnormal eye-head coordination in patients with schizophrenia. This can be considered as a starting point for further investigations, linking such results to psychopathology scales, investigating family members of patients to identify potential markers, or conducting longitudinal studies to establish possible predictors of treatment outcome. Also, to what degree abnormal eye-head coordination relates to motor, negative or positive symptoms must be clarified.

Clinical relevance

The examination of eye movements, sometimes also in consideration of head position and head movements are commonly applied in neurology. They are useful to check possible locations of lesions (Kennard, 2007). For example, vestibulo-ocular monitoring can predict the outcome after severe traumatic brain injury (Schlosser, Lindemann, Vajkoczy, & Clarke, 2009; Schlosser, Unterberg, & Clarke, 2005). In the last decade, the investigation of eye movements largely contributed in the field of psychiatric disorders, not only for a precise understanding of attentional and oculomotor symptoms, but also as potential diagnostic instrument. For example, exploratory eye movement are proposed for clinical diagnosis of schizophrenia with a sensitivity of 73% and a specificity of 79% (Suzuki et al., 2009). In a study by Benson et al. (2012) 98% of patients with schizophrenia could successfully be discriminated from controls just by eye movement behavioral data. In another study, clinical populations were classified during simply watching television (Tseng et al., 2013). However, a diagnostic instrument for schizophrenia solely based on oculography, or any other physiological measures such as neuroimaging techniques provide, may not take the whole picture for the moment, but they can provide additional information, for example towards the creation of empirical founded dimensions replacing the concept of subtypes. Instead of using subtypes (paranoid, catatonic, etc.), which have been removed in DMS-IV, the illness would rather be addressed using a defined set of dimensions along which everyone varies rather based on a category. A similar approach is used by Strik et al. (2010) to relate symptoms to three brain systems: the motor, language and limbic system. Such diagnostic approaches provide more information and more suitable as an instrument in research compared to subtypes. The major downside of subtypes or diagnostic categories is that it is built on an arbitrary chosen criterion dividing abnormal and normal (Peralta & Cuesta, 2007; Tsuang, Stone, & Faraone, 2000). Also, alternative approaches such as dimensional approaches would also be in concordance with the concept of schizotypy. In this respect, the study of eye-head coordination can contribute objective, empirical-driven information for the understanding of psychopathology

and the conception and validation of such dimensional scales. The study of eye-head coordination has also contributed to the understanding of other diseases, for example in movement disorders such as ataxia (Panouillères et al., 2013), or in epilepsy (McLachlan, 1987; Wyllie, Lüders, Morris, Lesser, & Dinner, 1986).

Further potential applications

Beside its clinical relevance, the study of eye-head shifts can contribute to many other domains. For example in robotics, building motorized camera head, or humanoid robots capable of conducting controlled gaze shifts (Law, Shaw, & Lee, 2013). A great effort is taken for the creation of autonomous intelligent mini-vehicles that visuo-spatially discover the surrounding environments (Doitsidis et al., 2012), most interesting for military and surveillance applications, which has to be critically questioned in view of ethical issues.

Another potential application is sports sciences. Visuomotor skills are a key factor in many sports. For example in baseball, hitting is a challenge for young players and requires experience over time. During hitting, within around 500 ms the batter fixates the ball and conducts a smooth pursuit eye movement to determine the trajectory of the ball and finally to perform a swing in order to hit it at the right spot. This has been studied in cricket players (Land & McLeod, 2000): primary interest was not to establish statistical inference upon a large study sample, but to investigate individual properties of single players. Such profiles may largely contribute individualized analysis and training for specific career development. In baseball, novice players tend to move their eyes before the release of the ball by the pitcher, or fixate another spot than the release point, for example the head (Shank & Haywood, 1987).

Eye-movement methodology can be combined with neuroimaging: For example, eye tracking was successfully combined with fMRI and transcranial magnetic stimulation to demonstrate a connection between visual exploration by the number of fixations and the fronto-parietal cortical network, and that this connection can be altered by stimulation (Chaves et al., 2012).

Last, eye-head coordination research can be applied in aging research to investigate elderly drivers. For example, testing visual acuity, visual field or any simple visual test without head movements may not account for the complexity of driving, where always both head and eye movement are performed (Gruber, Mosimann, Müri, & Nef, 2013).

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S.S.

Curriculum Vitae

Personal

Name	Simon Gabriel Schwab
Address	Department of Psychiatric Neurophysiology University Hospital of Psychiatry Bolligenstrasse 111 3000 Bern 60 Switzerland
Phone	+41 (0)31 930 9396
Email	`schwab@puk.unibe.ch`
Date of birth	March 11, 1980
Place of birth	Biel/Bienne (BE)
Nationality	Swiss
Place of residence	Bern
Place of origin	Kallnach (BE)

Education

2009 – 2013	Graduate School of Health Sciences (Neurosciences), University of Bern
10/2008	Master of Science (magna cum laude), University of Bern
2005 – 2008	Study of Computer Science (Minor), University of Bern
2000 – 2005	Study of Psychology (Major), University of Bern
1995 – 2000	Deutsches Gymnasium Biel, Matura Type C (Mathematics)

Employment

Since 07/2012	Computer Scientist, University Hospital of Psychiatry, University of Bern
Since 10/2008	Research Assistant, Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern
03/2008 – 06/2009	Research Assistant, Universitäre Fernstudien Schweiz
03/2007 – 09/2008	Undergraduate research assistant, IT Department, University of Bern
03/2007 – 09/2008	Undergraduate research assistant, Department of Psychology, University of Bern
04/2004 – 10/2004	Trainee, UNIX Services, IBM Switzerland, Winterthur
10/2001 – 03/2007	IT Assistant, Intercooperation, Bern

List of Publications

Articles published in peer-reviewed journals

Schwab, S., Würmle, O., & Altorfer, A. (2012). Analysis of eye and head coordination in a visual peripheral recognition task. *Journal of Eye Movement Research, 5*(2), 1–9. http://www.jemr.org/online/5/2/3

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Declaration of Originality

Last name, first name: **Schwab Simon**

Matriculation number: **00-121-186**

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.
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Bern, December 5, 2013

Simon Schwab