Visual perceptual stability and the processing of self-motion information: neurophysiology, psychophysics and neuropsychology

Visuelle perzeptuelle Stabilität und die Verarbeitung von Eigenbewegungsinformationen: Neurophysiologie, Psychophysik und Neuropsychologie

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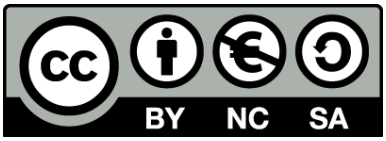

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Summary

While we move through our environment, we constantly have to deal with new sensory input. Especially the visual system has to deal with an ever-changing input signal, since we continuously move our eyes. For example, we change our direction of gaze about three times every second to a new area within our visual field with a fast, ballistic eye movement called a saccade. As a consequence, the entire projection of the surrounding world on our retina moves. Yet, we do not perceive this shift consciously. Instead, we have the impression of a stable world around us, in which objects have a well-defined location.

In my thesis I aimed to investigate the underlying neural mechanisms of the visual perceptual stability of our environment. One hypothesis is that there is a coordinate transformation of the retinocentric input signal to a craniocentric (egocentric) and eventually even to a world centered (allocentric) frame of reference. Such a transformation into a craniocentric reference frame requires information about both the location of a stimulus on the retina and the current eye position within the head. The physicist Hermann von Helmholtz was one of the first who suggested that such an eye-position signal is available in the brain as an internal copy of the motor plan, which is sent to the eye muscles. This so-called *efference copy* allows the brain to classify actions as self-generated and differentiate them from being externally triggered. If we are the creator of an action, we are able to predict its outcome and can take this prediction into consideration for the further processing. For example, if the projection of the environment moves across the retina due to an eye movement, the shift is registered as self-induced and the brain maintains a stable percept of the world. However, if one gently pushes the eye from the side with a finger, we perceive a moving environment. Along the same lines, it is necessary to correctly attribute the movement of the visual field to our own self-motion, e.g. to perform eye movements accounting for the additional influences of our movements. The first study of my thesis shows that the perceived location of a stimulus might indeed be a combination of two independent neuronal signals, i.e. the position of the stimulus on the retina and information about the current eye-position or eye-movement, respectively. In this experiment, the mislocalization of briefly presented stimuli, which is characteristic for each type of eye-movement, leads to a perceptual localization of stimuli within the area of the blind spot on the retina. Yet, this is the region where the optic nerve leaves the eye, meaning that there

are no photoreceptors available to convert light into neuronal signals. Physically, subjects should be blind for stimuli presented in this part of the visual field. In fact, a combination of the actual stimulus position with the specific, error-inducing eye-movement information is able to explain the experimentally measured behavior.

The second study in my thesis investigates the underlying neural mechanism of the mislocalization of briefly presented stimuli during eye-movements. Many previous studies using animal models (the rhesus monkey) revealed internal representations of eye-position signals in various brain regions and therefore confirmed the hypothesis of an efference copy signal within the brain. Although these eye-position signals basically reflect the actual eye-position with good accuracy, there are also some spatial and temporal inaccuracies. These erroneous representations have been previously suggested as the source of perceptual mislocalization during saccades. The second study of my thesis extends this hypothesis to the mislocalization during smooth pursuit eye-movements. We usually perform such an eye movement when we want to continuously track a moving object with our eyes. I showed that the activity of neurons in the ventral intraparietal area of the rhesus monkey adequately represents the actual eye-position during smooth pursuit. However, there was a constant lead of the internal eye-position signal as compared to the real eye-position in direction of the ongoing eye-movement. In combination with a distortion of the visual map due to an uneven allocation of attention in direction of the future stimulus position, this results in a mislocalization pattern during smooth pursuit, which almost exactly resembles those typically measured in psychophysical experiments. Hence, on the one hand the efference copy of the eye-position signal provides the required signal to perform a coordinate transformation in order to preserve a stable perception of our environment. On the other hand small inaccuracies within this signal seem to cause perceptual errors when the visual system is experimentally pushed to its limits.

The efference copy also plays a role in dysfunctions of the brain in neurological or psychiatric diseases. For example, many symptoms of schizophrenia patients could be explained by an impaired efference copy mechanism and a resulting misattribution of agency to self- and externally-produced actions. Following this hypothesis, the typically observed auditory hallucinations in these patients might be the result of an erroneously assigned agency of their own thoughts. To make a detailed analysis of this potentially impaired efference copy mechanism possible, the third study of my thesis investigated eye movements of

schizophrenia patients and tried to step outside the limited capabilities of laboratory setups into the real world. This study showed that results of previous laboratory studies only partly resemble those obtained in the real world. For example, schizophrenia patients, when compared to healthy controls, usually show a more inaccurate smooth pursuit eye-movement in the laboratory. Yet, in the real world when they track a stationary object with their eyes while they are moving towards it, there are no differences between patients and healthy controls, although both types of eye-movements are closely related. This might be due to the fact that patients were able to use additional sources of information in the real world, e.g. self-motion information, to compensate for some of their deficits under certain conditions.

Similarly, the fourth study of my thesis showed that typical impairments of eye-movements during healthy aging can be equalized by other sources of information available under natural conditions. At the same time, this work underlined the need of eye-movement measurements in the real world as a complement to laboratory studies to accurately describe the visual system, all mechanisms of perception and their interactions under natural circumstances. For example, experiments in the laboratory usually analyze particularly selected eye-movement parameters within a specific range, such as saccades of a certain amplitude. However, this does not reflect everyday life in which parameters like that are typically continuous and not normally distributed. Furthermore, motion-selective areas in the brain might play a much bigger role in natural environments, since we generally move our head and/or ourselves. To correctly analyze the contribution to and influences on eye-movements, one has to perform eye-movement studies under conditions as realistic as possible.

The fifth study of my thesis aimed to investigate a possible application of eye-movement studies in the diagnosis of neuronal diseases. We showed that basic eye-movement parameters like saccade peak-velocity can be used to differentiate patients with Parkinson's disease from patients with an atypical form of Parkinsonism, progressive supranuclear palsy. This differentiation is of particular importance since both diseases share a similar onset but have a considerably different progression and outcome, requiring different types of therapies. An early differential diagnosis, preferably in a subclinical stage, is needed to ensure the optimal treatment of the patients in order to ease the symptoms and eventually even improve the prognosis. The study showed that mobile eye-trackers are particularly

well-suited to investigate eye movements in the daily clinical routine, due to their promising results in differential diagnosis and their easy, fast and reliable handling.

In conclusion, my thesis underlines the importance of an interaction of all the different neuroscientific methods such as psychophysics, eye-movement measurements in the real world, electrophysiology and the investigation of neuropsychiatric patients to get a complete picture of how the brain works. The results of my thesis contribute to extent the current knowledge about the processing of information and the perception of our environment in the brain, point towards fields of application of eye-movement measurements and can be used as groundwork for future research.

Zusammenfassung

Während wir uns durch unsere Umwelt bewegen, sind wir ständig neuen Sinneseindrücken ausgesetzt. Insbesondere das visuelle System erhält fortwährend neue Informationen zur Verarbeitung, da wir unsere Augen nahezu ständig bewegen. Beispielsweise richten wir etwa dreimal pro Sekunde unseren Blick mit einer schnellen Augenbewegung, einer sogenannten Sakkade, auf einen neuen Bereich in unserem visuellen Feld. Dabei verschiebt sich das gesamte Abbild unserer Umwelt auf der Netzhaut (Retina) der Augen. Dennoch nehmen wir diese Verschiebung nicht bewusst wahr. Stattdessen haben wir den Eindruck einer stabilen Welt um uns herum, in der Objekte einen festen Platz haben.

Meine Dissertation beschäftigt sich zunächst mit der Frage, welche Mechanismen dem Gehirn diese perzeptuelle Stabilität unserer Umwelt ermöglichen. Eine weit verbreitete These ist, dass dazu eine Koordinatentransformation des retinalen Abbildes in ein kopfzentriertes (egozentrisches) oder letztendlich sogar weltzentriertes (allozentrisches) Referenzsystem stattfindet. Für die Umwandlung von retinalen Koordinaten in kopfzentrierte Koordinaten benötigt man neben der Position eines Stimulus auf der Netzhaut auch Informationen über die gegenwärtige Position der Augen im Kopf. Der Physiker Hermann von Helmholtz war einer der Ersten, der bereits im 19. Jahrhundert vorschlug, dass dieses Augenpositionssignal als interne Kopie des Bewegungsbefehls an die Augenmuskeln anderen Arealen im Gehirn zur Verfügung gestellt wird. Dieses *Efferenzkopie* genannte Signal gibt dabei dem Gehirn die Möglichkeit, eine Handlung als selbstgeneriert zu klassifizieren und von einer extern generierten Bewegung zu unterscheiden. Sind wir selbst der Urheber einer Handlung, können wir deren Folgen vorhersagen und dies bei der weiteren Verarbeitung entsprechend berücksichtigen. Verschiebt sich also beispielsweise das Abbild unserer Umwelt auf der Retina in Folge einer Augenbewegung, registriert das Gehirn dies als selbstinduziert und erhält die Wahrnehmung der Außenwelt stabil. Drückt man jedoch sanft von außen gegen seinen Augapfel, kann man beobachten, wie sich die Umgebung scheinbar bewegt. In gleicher Weise ist es wichtig für uns, die Bewegung des visuellen Feldes unserer Bewegung durch die Umwelt korrekt zuzuordnen, um beispielsweise Augenbewegungen so auszuführen, dass sie die zusätzlichen Einflüsse unserer Eigenbewegung berücksichtigen. Die erste Studie meiner Arbeit zeigt, dass der wahrgenommene Ort von Reizen im Gehirn, tatsächlich wie angenommen, durch die

Kombination zweier unabhängiger Signale gebildet werden könnte, nämlich der Position des Abbildes eines Reizes auf der Retina und der Information über die gegenwärtige Augenposition resp. -bewegung. Dabei sorgte die für jede Augenbewegung typische Fehllokalisation von kurz eingeblendeten Reizen dafür, dass Versuchspersonen Stimuli in den sogenannten Blinden Fleck verorteten. Dies ist der Bereich der Netzhaut, an dem der Sehnerv das Auge verlässt, weshalb dort keine Photorezeptoren zur Umwandlung von Licht in neuronale Signale zur Verfügung stehen. Physikalisch können die Versuchspersonen also dort keine Reize wahrnehmen. Eine Kombination der tatsächlichen Reizposition mit der spezifischen, fehlerinduzierenden Augenbewegungsinformation erklärt das gezeigte Verhalten jedoch sehr gut.

Die zweite Studie meiner Dissertation untersucht die neuronale Ursache der Fehlwahrnehmung von kurz eingeblendeten Reizen während Augenbewegungen. Viele Studien am Tiermodel (Rhesusaffe) konnten bereits zuvor interne Repräsentationen von Augenpositionssignalen in unterschiedlichen Hirnarealen nachweisen und untermauerten damit die Hypothese der Existenz einer Efferenzkopie im Gehirn. Gleichwohl fand man heraus, dass dieses interne Signal zwar grundsätzlich die tatsächliche Augenposition sehr gut widerspiegelt, es jedoch räumliche und zeitliche Ungenauigkeiten aufweist. Diese fehlerhafte Repräsentation wurde als mögliche Ursache für die Fehlwahrnehmung während Sakkaden vorgeschlagen und in meiner zweiten Studie auf die Fehlwahrnehmung während glatter Augenfolgebewegungen ausgeweitet. Eine solche Augenbewegung führt man aus, wenn man ein sich bewegendes Objekt dauerhaft mit seinen Augen verfolgt. Ich konnte zeigen, dass die neuronale Aktivität im ventralen intraparietalen Areal des Rhesusaffen die Augenposition während glatter Augenfolgebewegung angemessen abbildet, die interne Repräsentation jedoch der tatsächlichen Augenposition vorauseilt. In Kombination mit einer Verzerrung der visuellen Abbildung durch eine ungleichmäßige Verteilung der Aufmerksamkeit in Richtung der zukünftigen Stimulusposition ergibt sich ein Fehllokalisationsmuster, welches dem psychophysikalisch gemessenen Muster nahezu exakt entspricht. Die Efferenzkopie der Augenbewegungsinformation dient somit einerseits als notwendiges Signal zur Koordinatentransformation im Gehirn und damit zum Erhalt der wahrgenommenen Stabilität unserer Umwelt. Auf der anderen Seite scheinen jedoch Ungenauigkeiten in diesem Signal Wahrnehmungsfehler zu verursachen, sobald wir das visuelle System im Experiment an seine Grenzen bringen.

Die Efferenzkopie spielt auch bei Fehlfunktionen im Gehirn bei neurologischen oder psychiatrischen Krankheiten eine Rolle. So lassen sich beispielweise viele Symptome von Schizophreniepatienten auf einen beeinträchtigten Efferenzkopie-Mechanismus und damit einer fehlerhaften Zuordnung von Eigen- und Fremdhandlungen zurückführen. Die typischerweise auftretenden auditorischen Halluzinationen könnten beispielsweise lediglich das Resultat einer falschen Zuordnung von eigenen Gedanken sein. Um eine gezieltere Untersuchung der möglicherweise fehlerhaften Efferenzkopie zu ermöglichen, erforschte die dritte Studie in meiner Dissertation die Augenbewegungen von Schizophreniepatienten und versucht dabei den Schritt aus den limitierten Möglichkeiten im Labor in die reale Welt zu machen. Dabei zeigte sich, dass die Ergebnisse aus früheren Studien im Labor nur teilweise auf natürliche Umgebungen übertragen werden können. Unter anderem zeigen Schizophreniepatienten im Labor eine ungenauere glatte Augenfolgebewegung als gesunde Kontrollprobanden. Wenn sie jedoch in der realen Welt ein stationäres Ziel mit den Augen verfolgen, auf das sie sich zubewegen, zeigen sich keinerlei Unterschiede mehr zwischen Patienten und Kontrollprobanden, obwohl beide Arten von Augenbewegungen sehr eng miteinander verwandt sind. Wir schlussfolgerten daraus, dass Patienten zusätzliche Informationsquellen, beispielsweise über ihre Eigenbewegung, nutzen können, um unter gewissen Voraussetzungen einige ihrer Defizite auszugleichen.

In ähnlicher Weise zeigte die vierte Studie meiner Dissertation, dass auch typische Beeinträchtigungen von Augenbewegungen im Alter unter natürlichen Bedingungen mit Informationen aus anderen Quellen teilweise kompensiert werden können. Gleichzeitig verdeutlichte diese Studie die Wichtigkeit von Untersuchungen in der realen Welt als Ergänzung zu Messungen im Labor, um das visuelle System und alle Mechanismen der Wahrnehmung in ihrem natürlichen Zusammenspiel abzubilden. So werden im Labor häufig lediglich speziell ausgewählte Augenbewegungsparameter wie Sakkaden mit einer gewissen Amplitude untersucht. Dies spiegelt jedoch nicht das Verhalten im alltäglichen Leben wider, in dem solche Größen üblicherweise kontinuierlich und nicht normalverteilt sind. Des Weiteren kommt in natürlichen Umgebungen den Bereichen im Gehirn, die Bewegungsinformationen verarbeiten, eine besondere Rolle zu, da wir meist unseren Kopf oder uns selbst bewegen. Um die damit verbundenen Beiträge und Einflüsse auf Augenbewegungen korrekt zu untersuchen, ist die Analyse von Augenbewegungen unter möglichst realen Voraussetzungen nötig.

Die fünfte Studie in meiner Dissertation untersucht einen möglichen praktischen Anwendungsbereich von Augenbewegungsmessungen zur Diagnose von neuronalen Erkrankungen. Dabei konnte gezeigt werden, dass grundlegende Parameter wie die Spitzengeschwindigkeit einer Sakkade genügen, um Patienten mit Parkinson und einer atypischen Form der Parkinsonkrankheit, der progressiven supranukleären Blickparese, von einander zu unterscheiden. Dies ist von besonderer Bedeutung, da beide Krankheiten einen sehr ähnlichen Beginn, jedoch im Folgenden einen sehr unterschiedlichen Verlauf und Ausgang haben, wodurch unterschiedliche Therapien notwendig sind. Eine frühzeitige Differentialdiagnose, möglichst bereits im subklinischen Stadium, ist unumgänglich, um die optimale Behandlung der Patienten zu gewährleisten, damit auftretende Symptome gelindert werden können oder möglicherweise sogar die Prognose verbessert werden kann. Dabei erwiesen sich mobile Augenbewegungsmessgeräte aufgrund ihrer vielversprechenden Ergebnisse bei der Differentialdiagnose und der einfachen, schnellen und zuverlässigen Handhabung als besonders geeignet für den klinischen Alltag.

Insgesamt unterstreicht meine Dissertation die Wichtigkeit des Zusammenwirkens der unterschiedlichen neurowissenschaftlichen Methoden wie Psychophysik, Augenbewegungsmessungen in natürlichen Umgebungen, Elektrophysiologie und die Untersuchung von neuropsychiatrischen Patientengruppen, um ein vollständiges Bild davon zu erhalten, wie das Gehirn funktioniert. Die Ergebnisse meiner Arbeit tragen dazu bei, das bisherige Wissen über die Informationsverarbeitung und Wahrnehmung im Gehirn zu erweitern, zeigen Anwendungsgebiete von Augenbewegungsmessungen auf und können als Grundlage für zukünftige Forschungen genutzt werden.

1. Introduction

Our brain is continuously exposed to external sensory stimuli and has to handle and process them in order to interact with our environment. The main sensory input of primates is the visual sense (Palmer, 1999) which uses the eyes and the retina, including photosensitive cells called cones and rods, to analyze information contained in visible light.

One functional property of the eyes that stands out among the other sensory organs is the ability to move. We constantly make eye movements to analyze certain aspects of our visual field with the part of the retina with the highest possible resolution, the fovea. About three times per second (Rayner, 1998; Land, 1999), that is more often than our heart beats, we change our gaze with a fast, ballistic eye movement called saccade (Carpenter, 1988). Moreover, we are able to keep moving objects within the fovea using smooth tracking eye-movements. For this, it is not important if the objects move themselves or if their projection moves across the retina due to our self-motion. Despite the numerous eye movements we perform every second, we perceive the world around us as stable. Furthermore, our perception of the world is complete, although there is an area on our retina without any photoreceptors, called the blind spot. The underlying neuronal and behavioral mechanisms of these and many other remarkable perceptual effects are a topic of research for a long time during which the visual system has been proven to serve as a window to the brain (Gompel, 2007). Additionally, the fact that our visual system shares a lot of commonalities with non human primates (Fuchs, 1967; Bremmer et al., 2001; Orban et al., 2004; Solomon & Rosa, 2014) offers a great opportunity to perform electrophysiological recordings in the animal model to complement behavioral experiments in humans and gain insight to the function of certain brain regions at the cellular level. Since some aspects and neuronal correlates of eye-movements are already well explained, we are able to transfer this knowledge to new applications to gain new insights to previously unknown mechanisms and even investigate neurological and psychological diseases and their underlying neuronal dysfunctions. Yet, there are still many open questions, especially when one tries to step outside of the laboratory to study eye-movements and the visual system without restrictions in natural environments.

In this thesis I aimed to investigate the mechanisms underlying the stable and complete perception of our environment using psychophysical and electrophysiological methods.

Moreover, I tried to gain new insights and verify the transferability of knowledge to new fields of eye tracking and clinical research in the real world. The sections below will give a short introduction to the general function of the visual system. A more specific introduction to the different topics of this thesis can be found in the respective sections.

1.1. The Retina

In the retina two types of photoreceptors, rods and cones, absorb visible light. There are three different types of cones: S-, M-, & L-Cones each absorbing light within a specific range of wavelengths. According to the absorption maxima, cones typically are named blue, green and red, respectively. Rods and cones are differently distributed across the retina (Figure 1). The area with the highest density of cones is called the fovea and marks the spot with the highest visual acuity.

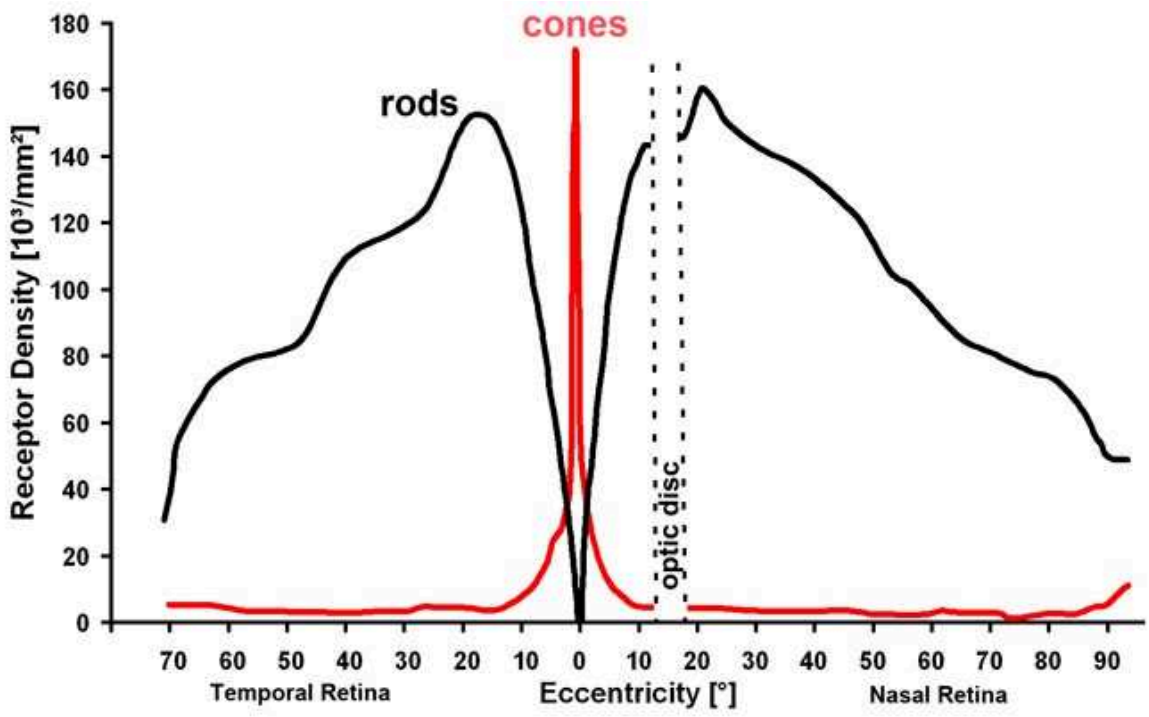

Figure 1: *Distribution of Rods and Cones in the retina as a function of distance from the fovea, marked by the position with the highest density of cones. The blind spot / optic disc is characterized by the absence of any photoreceptors. Modified from* Webvision (http://webvision.med.utah.edu/) after (Osterberg, 1935).

The area with no photoreceptors is called the blind spot or optic disc. It is located about 15° nasal of the fovea and about 2° below the horizontal meridian in every human and has a highly variable size between 8.0° – 13.7° in vertical direction and 6.1° – 9.6° in horizontal direction, depending on the subject (Armaly, 1969). In this area no visual input can be registered. Yet, humans have a complete representation of the outside world. During binocular vision the visual information registered from one eye compensates for the "Null information" in the region of the blind spot of the other eye. But even during monocular vision we have a complete perception of our environment. This is accomplished by a mechanism called "Filling-In" (Budge, 1862), which integrates visual information from the surrounding of the blind spot to supplement perception. At the point of the blind spot the optical nerve leaves the eye and the further processing of visual information is split into two distinct pathways, the magnocellular- (M) and the parvocellular-pathway (P), which eventually reach the primary visual cortex (Sawatari & Callaway, 1996). Here, the blind spot is represented topographically correct and fits seamlessly with the visual representation of our environment (Fiorani et al., 1992).

1.2. Visual pathways and motion selective areas

The M-pathway mainly processes higher temporal and lower spatial frequencies, luminance contrasts and carries orientation- and direction-selective information. Therefore, it provides the information to analyze moving stimuli, including the location within visual space, detection of visual change and plays a crucial role in controlling eye movements (Bullier, 2001; Lamme & Roelfsema, 2000; Nowak et al., 1997; Vidyasagar, 1999). The P-pathway, on the other hand, processes higher spatial frequencies and encodes information about shape, size or color (Merigan & Maunsell, 1993). On their way to the primary visual cortex the two separate pathways from each eye cross at the optic chiasm in a way that information in the left visual field is processed in the right primary visual cortex and vice versa (Figure 2). Thus, each hemisphere processes its contralateral hemifield.

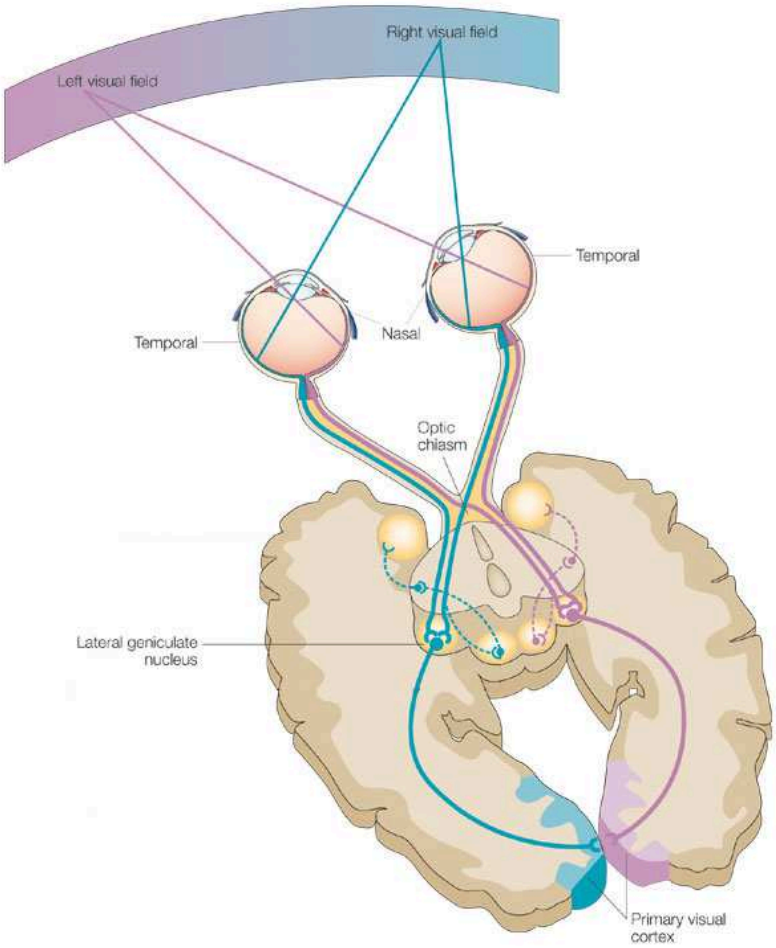

Figure 2: *Schematic overview of the hemispheric processing of visual information from the retina to the primary visual cortex through the optic chiasm and the lateral geniculate nucleus (LGN). Modified from Hannula et al. 2005.*

The lateral geniculate nucleus (LGN) represents the next processing stage before the visual information eventually reaches the primary visual cortex (V1). From this point on the separation of the M- and P-pathway becomes less strict and the processing of visual information can be categorized to the dorsal- and ventral stream (Goodale & Milner, 1992). The ventral stream (also called 'what pathway') receives input from M- and P-pathways and encodes object features like size, color or borders. The dorsal stream mainly receives magnocellular input (Ferrera et al., 1994) and represents spatial- and motion information, for which it is also called the 'where pathway'. The areas along both pathways are not separated and share many connections between them (Felleman & Essen, 1991). Figure 3 gives a schematic overview of some key areas, which are mainly involved in the processing of visual motion information and are therefore of specific relevance for this thesis.

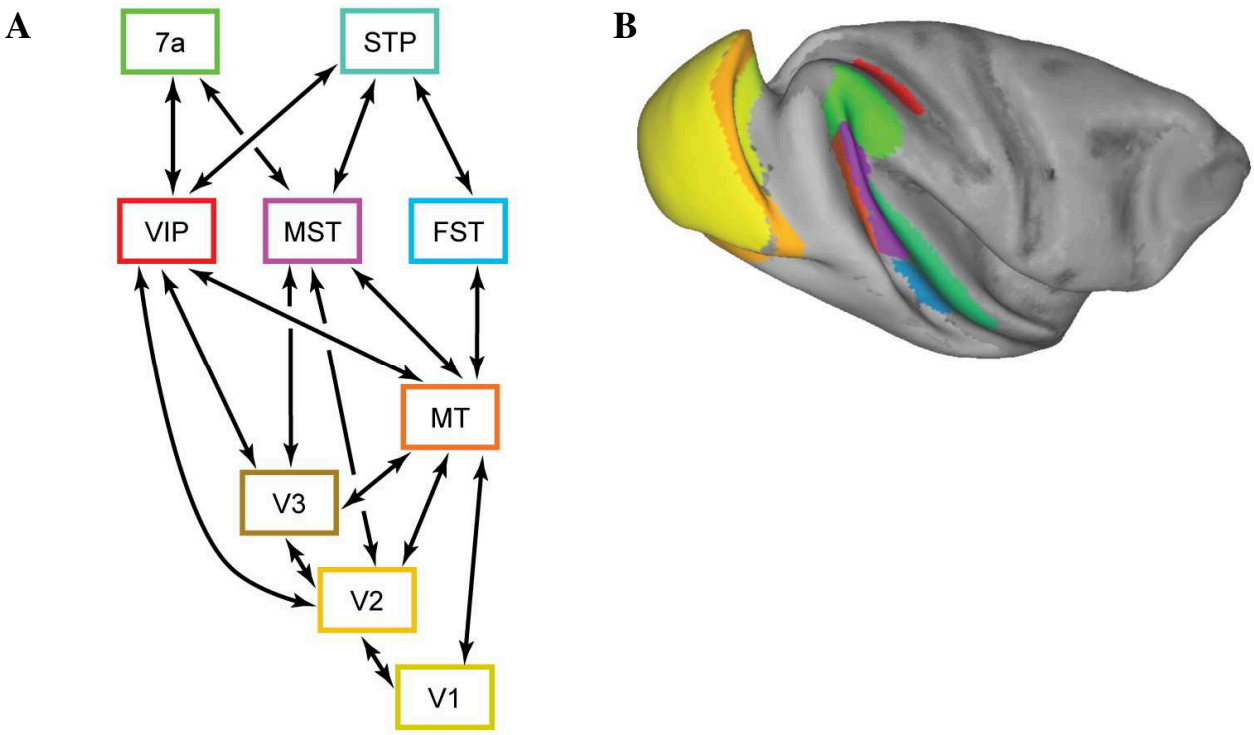

Figure 3: *A: Schematic overview of areas of the cortex of the macaque monkey involved in the processing of visual motion information and their connections among each other. B: Anatomical locations of the areas in the macaque brain. V1: primary visual cortex, V2: secondary visual cortex, V3: tertiary visual cortex, MT: middle temporal area, MST: medial superior temporal area, VIP: ventral intraparietal area, FST: fundal area of the superior temporal sulcus, 7a: Brodmann area 7a, STP: superior temporal polysensory area. After Britten (2008).*

Along the dorsal stream the middle temporal area (MT) marks the first important part of the visual motion system with its neurons encoding motion direction and speed (Maunsell & Essen, 1983; Newsome & Pare, 1988). Further along the dorsal stream the medial superior temporal area (MST) gets more involved in the global aspects of visual motion integrating optic flow information, which is present when one moves trough the environment (Gibson, 1950; Figure 4), with vestibular- and extraretinal eye-position signals (Duffy & Wurtz, 1991; Bremmer et al., 1999; 2010).

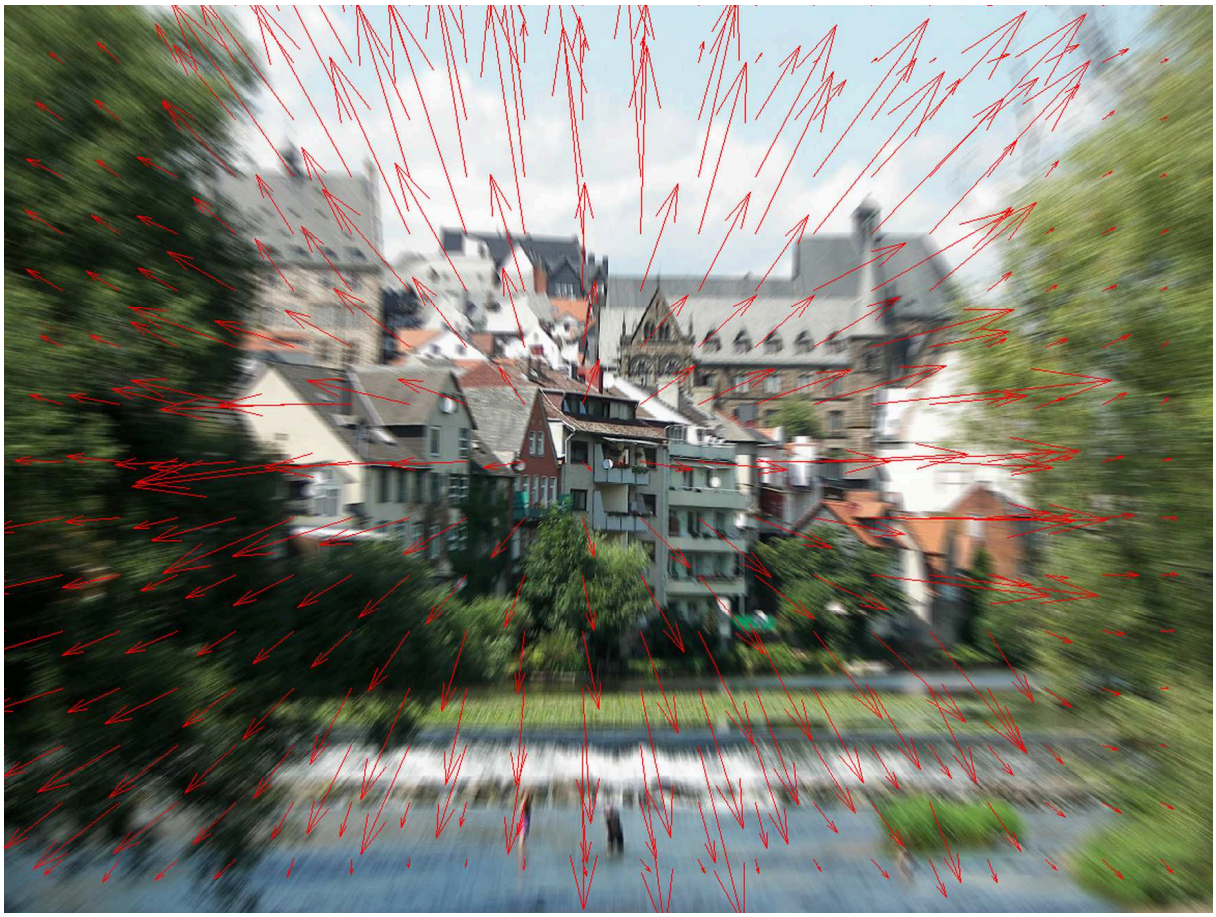

Figure 4: *Illustration of an optic flow field projected on the retina generated by self-motion trough a natural environment. Red arrows indicate the local motion direction with the length correlating to the speed. The part of the image with no local motion, here the center, is called the focus of expansion (FoE) and corresponds under certain conditions to the direction of self-motion.*

Finally the multimodal ventral intraparietal area (VIP) is a key area for the processing of self-motion by decoding global motion and heading information (Bremmer, 2005; Chen et al., 2011) as well as coordinating smooth eye and head movements within near-extrapersonal space (Schlack et al., 2003; Bremmer et al., 2013). Most neurons in area VIP are tuned for one or even multiple types of optic flow stimuli, e.g. radial flow, frontoparallel flow, or rotating stimuli (Bremmer et al., 2002a). In this area visual, vestibular, tactile and auditory information is combined (Avillac et al., 2005, 2007; Bremmer et al., 2002a, 2002b; Chen et al., 2011; Duhamel et al., 1998; Schlack et al., 2002). It contains neurons encoding spatial information in eye-centered, head-centered and intermediate reference frames (Schlack et al., 2005). This functional property most likely plays a crucial role in the coordinate transformation of the retinocentric visual input to a head-centered frame of reference, allowing a more stable perception of the environment. The versatility of area VIP got

extended further by a study of Cooke and colleagues (2003), which showed that electrical microstimulation in this area elicited typical avoidance or defense reactions, which could also be triggered by tactile stimulation of the monkeys' cheek with air blows.
Areas even higher in the processing hierarchy like Brodmann area 7a or the superior temporal polysensory area (STP) encode more and more complex and specific aspects of motion information (Britten, 2008). For example, area STP eventually combines information from the dorsal and ventral stream to encode three-dimensional surface structures and structure-from-motion (Anderson & Siegel, 2005).

1.3. Efference copy

In order to correctly attribute the agency of an action, e.g. to determine if motion in the visual field is caused by an external motion or due to self-motion, the brain requires additional, non-retinal information. If a movement of the visual field is self-produced by an eye-movement, the brain could use predictive mechanisms in order to anticipate the accompanying effects (Blakemore et al., 2000). Such a system would be able to perceptually compensate the movement of the image on the retina during an eye movement and thus generate a stable perception of our environment. Von Helmholtz (1866) was the first to propose an internal copy of an outgoing motor command controlling the eye muscles in order to correctly localize an object relative to the head. This internal representation of an extraretinal signal about an ongoing eye-movement has been termed "efference copy" (von Holst & Mittelstaedt, 1950) or "corollary discharge" (Sperry, 1950). Indeed, such an efference copy signal can be found in many areas in the primate brain in which neurons modulate their firing rate according to changes of the current gaze direction (parietal cortex: Andersen & Mountcastle, 1983; Bremmer et al. 1997b, 1999; Morris et al. 2012, 2013; striate cortex: Trotter and Celebrini, 1999; extrastriate cortex: Galletti & Battaglini, 1989; Bremmer et al. 1997a; premotor cortex: Boussaoud et al., 1998). Recent studies in dorsal visual areas of the macaque monkey have proven the feasibility to decode actual eye positions (Bremmer et al., 1998, Boussaoud & Bremmer, 1999; Morris et al., 2012, 2013) solely from recorded neuronal discharges. This relationship has been termed "gain fields" or "eye-position fields". These gain fields are thought to be crucial for a stable perception of our environment by providing the information required to transform the retinocentric visual

input into a non-retinocentric frame of reference (Snyder et al., 1998; Salinas & Abbott, 2003), e.g. cranio-centric, by combining information about the location of a stimulus on the retina with information about the current eye position (Zipser & Andersen, 1988; Bremmer et al., 1998).

1.4. Eye movements

Eye movements can be separated into two different classes, reflexive and foveating. In the first class, the vestibulo-ocular reflex (VOR) and the optokinetic nystagmus (OKN) serve to stabilize the image of the outside-world on the retina during head movements or self-motion (Ilg, 1997). During natural behavior, both types of eye-movements complement each other in order to ensure optimal performance. Thereby, VOR primarily controls compensatory eye-movements to fast head rotations with extremely short latencies of about 10 ms (Aw et al., 1996), whereas OKN counterbalances an external large-scale motion of the visual field to stabilize gaze (Lappe & Hoffmann, 2000).

In my thesis foveating eye movements are of particular interest, among them saccades fixational and smooth pursuit eye-movements. Saccades are fast, ballistic, goal directed eye-movements to change the gaze to different parts of the visual field. They can be controlled voluntarily and reach amplitudes of up to 80° (Carpenter, 1988). Saccades to visual targets are usually elicited within a certain reaction time (latency) with a mean of about 200ms and a speed of up to 900°/s (Kandel, Schwartz & Jessell, 2000). These saccade dynamics are rather standardized, i.e. there is a fixed relationship between saccade amplitude and duration or amplitude and velocity called the *main sequence,* which follows a power function and can be linearly approximated for saccades of up to 15° (Bahill et al., 1975). Additionally, there are multiple perceptual phenomena accompanying saccades. Saccadic suppression is thought to maintain perceptual stability throughout the fast changing retinal motion during saccades by a selective reduction of detection sensitivity of transient stimuli (Diamond et al., 2000). A neural basis of this perceptual phenomenon has been identified in the animal model in motion sensitive areas of the dorsal pathway (Bremmer et al., 2009). Furthermore, visual stimuli briefly presented around the time of a saccade are spatially mislocalized (Honda, 1991; Dassonville et al., 1992). A neuronal basis for this perceptual error has been proposed only recently. Morris and colleagues suggested that this spatial mislocalization is

based on rapidly updated but imperfect eye-position signals in the dorsal visual system (Morris et al., 2012).

Fixational eye-movements serve to keep a stationary object on the fovea when the observer does not move. Typically, they are a mixture of micro-saccades, tremor and drift with a general activity of the eye muscles (Martinez-Conde et al., 2004), and hence are classified as eye movements. In 1935, Buswell was one of the first who investigated fixational patterns of participants viewing different pictures and found great differences depending on the stimulus presented as well as the given task, which was later confirmed by an influential study of Yarbus (1967), suggesting that eye movements are influenced by cognitive processes. In general, fixation timing and duration is highly modulated by the information aimed to acquire (Ballard et al., 1992) and the experimental setting (e.g. mean fixation duration when viewing an urban environment of 375ms vs. 440 ms when viewing a forest; Pelz & Rothkopf, 2007).

When viewing still scenes, we usually perform an alternation of saccades and fixations (Yarbus, 1967), but if the observer starts moving trough his/her environment another type of eye movement is necessary to keep a stationary object on the fovea. The resulting smooth tracking eye-movements try to compensate the motion of the whole visual field in order to stabilize the image of the stationary object on the fovea. This third type of eye movement has not been extensively studied so far, for which this thesis aims to fill the gap.

Finally, smooth pursuit eye-movements (SPEM) of a moving object are thought to be related to smooth tracking eye-movements as they serve the same purpose: keep an object stable on the fovea. Different from tracking of a stationary target during self-motion, here the observer is stationary and the object of interest moves. Similar to saccades, targets briefly flashed during smooth pursuit are mislocalized, but this time almost exclusively in direction of the pursuit target and within the visual hemifield ahead of pursuit (Mateeff et al., 1981; van Beers et al. 2001; Bremmer und Königs, 2010). SPEM heavily relies on the presence of a moving visual target (Robinson, 1965), using the visual motion information on the retina together with extraretinal information about the current eye movement and eye position to closely match the velocity of the eye to the target velocity to provide the most stable image of the target on the retina (Ilg, 1997; Thier & Ilg, 2005). To evaluate the quality of SPEM, researchers typically use the gain, which is calculated by dividing eye velocity by target velocity leading to a value of 1.0 for optimal following of the target. A dysfunction within the

smooth pursuit system resulting in a decreased gain is a well-studied manifestation of certain brain dysfunctions accompanying not only brain diseases (e.g. Holzman et al., 1974; Holzman, 2000) but also healthy aging (Ross et al., 1999).

1.4.1. Eye movements – A window to the brain

For more than 100 years, eye movements and their dysfunctions where utilized by researchers to investigate general brain functions (e.g. Helmholtz, 1866; Dodge, 1903; Yarbus, 1967) and specific impairments in diseases like schizophrenia or Parkinson's disease (e.g. Diefendorf & Dodge, 1908; DeJong & Jones, 1971; Leigh & Zee, 2006). The noninvasive, reliable, rapid and simple measurement of eye movements offers the unique opportunity to gain deeper insights to the underlying mechanisms of brain functions, since some basic aspects are already well studied and neuronal correlates of certain eye-movement features have been identified previously (Ilg, 1997; Leigh & Kennard, 2004; Krauzlis, 2004). A lot of this knowledge originates from work on the animal model, non-human primates (NHP). Due to its considerable similarity to humans in regards of the visual system it is possible to extrapolate results of single cell recordings, which could hardly be obtained otherwise, from monkeys to men (Fuchs, 1967; Felleman & van Essen, 1991; Bremmer et al., 2001; Orban et al., 2004; Solomon & Rosa, 2014). This analogy allows to reliably identify neuronal correlates of specific aspects of vision, from the neuronal basis of eye movements (Krauzlis, 2004; Thier & Ilg, 2005) to more cognitive processes like attention (Treue, 2001). With this knowledge it is possible to trace specific areas in the brain using eye movement deviations or abnormalities, which can be observed in many different brain diseases (Leigh & Zee, 2006) or elicited artificially in psychophysical experiments of healthy participants by pushing the visual system to its limit (Fechner, 1860; Gescheider, 2013). As a result, the sole measurement of eye movements is capable of identifying possible sources of neuropsychological or neurological diseases as well as extending the knowledge of specific aspects of vision in the healthy brain. In the long-run, eye movements might even provide objective parameters to support the diagnosis of specific brain diseases in the clinical routine.

Furthermore, not only brain diseases, but also the changes in the brain and its functions throughout healthy aging can be investigated by studying eye movements. These

measurements can help gaining insights into the underlying neuronal mechanisms of senescence, since eye movements (Morgan, 1993; Moschner & Baloh, 1994) as well as perception (e.g. self-motion perception: Billino et al., 2008; Lich & Bremmer, 2014) are altered as we are getting older. Additionally many brain disorders often manifest themselves in particular periods of life, e.g. Alzheimer's and Parkinson's disease in the elderly (Corder et al., 1993; Hoehn & Yahr, 1998). To identify the specific alterations caused by these disorders, it is necessary to fully understand common changes caused by healthy aging.

In the last decades, most eye-movements studies have been performed in the laboratory with artificial visual stimuli, since they can be easily controlled. However, with the growing availability of mobile eye-trackers in the recent years, scientists began to step outside the laboratory and overcome its limitations to examine eye movements in the real world and check to what extent common findings in the laboratory can be transferred to activities of daily living.

1.4.2. Eye movements in the real world

Recent studies on eye movements comparing results from the laboratory with those from real-world scenarios found significant differences ('t Hart et al., 2009; Foulsham et al., 2011; Tatler et al., 2011). Moreover, eye movements in the real world are generally more variable depending on the environment (Einhäuser et al., 2007; Pelz & Rothkopf, 2007; 't Hart and Einhäuser, 2012) or the task (Land et al., 1999; Hayhoe, 2000). Without a specific task eye movements are mainly performed along the four cardinal directions (up, down, left, right) (Einhäuser et al., 2007). These findings raised substantial doubt concerning a general transferability of results from eye-movement measurements in the laboratory to the real world. Simultaneously they underline the need to understand oculomotor behavior in natural environments. Results from such studies will provide insight into the systems that govern specific eye movements and the neural mechanisms controlling them.

In contrast to the restrained conditions in the laboratory, eye movements in more natural settings are typically accompanied by head movements (Land 1992; Einhäuser et al., 2009). In this joint occurrence eye movements often compensate for head movements to stabilize gaze or aid head movements in performing huge gaze shifts (Guitton, 1992; Goossens & Van Opstal, 1997). Furthermore, participants in laboratory setups are usually artificially deprived

of additional sensory input other then the isolated aspect under investigation, whereas information processing of the visual system in the real world has to cope with additional sensory stimulations like visual, vestibular, auditory and tactile information. These diverse input resources not only challenge the brain, but also give the opportunity to compensate specific deficits in the one domain with information provided by other sources. Another huge difference between eye movements in the laboratory and the real world is that in everyday life eye movements are often accompanied by a person's self-motion. While moving, the eye-movement control system encounters different demands than during still sitting. For example, a fixational eye-movement of a stationary target in the laboratory turns into a smooth tracking eye-movement during self-motion (Niemann et al., 1999). Likewise, during free real-world movements plain smooth pursuit eye-movements are accompanied by head movements and have to integrate self-motion information in order to perform optimally. However, due to the self-motion the visual system has access to additional sensory information, e.g. optic flow (Gibson, 1950; see figure 4).

All those differences of eye-movements in everyday life compared to the restricted but well controlled laboratory measurements suggest a substantially bigger involvement of cortical areas in the parietal cortex, which primarily processes self-motion information (Bremmer et al., 2000), during natural behavior. In this context, the multimodal area VIP, for which a functional equivalent has been identified in humans (Bremmer et al., 2001), might be of particular importance as a central source and constructor of multiple signals regarding eye movements and self-motion.

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2. Studies

2.1. Overview

Study 1:

Monocular visual localization during eye movements

Stefan Dowiasch, Janne van Aswegen & Frank Bremmer

In preparation

Study 2:

Neural basis of spatial mislocalization during smooth eye-movements

Stefan Dowiasch, Gunnar Blohm & Frank Bremmer

In preparation

Study 3:

Eye movements of patients with schizophrenia in a natural environment

Stefan Dowiasch, Bianca Backasch, Wolfgang Einhäuser, Dirk Leube, Tilo Kircher & Frank Bremmer

European Archives of Psychiatry and Clinical Neuroscience 2014:1-12. doi:10.1007/s00406-014-0567-8

Study 4:

Effects of Aging on eye movements in the real world

Stefan Dowiasch, Svenja Marx, Wolfgang Einhäuser & Frank Bremmer

Frontiers in Human Neuroscience 9:46 (2015). doi: 10.3389/fnhum.2015.00046

Study 5:

Validation of mobile eye-tracking as novel and efficient means for differentiating progressive supranuclear palsy from Parkinson's disease

Svenja Marx, Gesine Respondek, Maria Stamelou, Stefan Dowiasch, Josef Stoll, Frank Bremmer, Wolfgang Oertel, Günther Hoglinger & Wolfgang Einhauser

Frontiers in Behavioral Neuroscience 2012;6. doi:10.3389/fnbeh.2012.00088

2.2. Motivation and scopes of the studies

In this thesis I conducted five studies using psychophysical, neurophysiological and neuropsychological techniques with the aim to investigate how the brain creates a stable, continuous and complete perception of our environment and how commonly known aspects of vision and specifically eye movements transfer from constrained laboratory setups to the real world. Eye movements challenge the visual system and a stable perception of our environment (Bremmer & Krekelberg, 2003) not only by a constantly changing input signal, but also through additional distortions of the field of view via head movements and self-motion.

The first study utilized psychophysics to investigate the phenomenon of a continuous and complete perception of our environment throughout different kinds of eye movements despite the presence of the blind spot, the area on the retina with no visual input. This study tried to provoke a perceptual mislocalization associated with eye movements into a region we are physically blind for. More specifically, I aimed to determine if, how and at what processing stage retinal information is combined with extraretinal information to perform a coordinate transformation of visual signals into a non-retinotopic frame of reference.

In the second study I performed a computational analysis of behavioral and neuronal data recorded in two NHPs to examine the efference copy mechanism of eye-position signals in the NHP model. This mechanism of an internal representation of current eye-position is thought to be an essential component for generating the stable perception of our environment. It is suggested (Zipser & Andersen, 1988; Bremmer et al., 1998) that these signals are neutrally combined with information about the retinal location of a stimulus to perform a coordinate transformation from the retinocentric input signal of the eyes to a head-centered frame of reference. Furthermore, inaccuracies in this internal eye-position signal might explain behaviorally measured mislocalizations of briefly presented stimuli during various types of eye movements.

The other three studies focused on eye movements in the real world and investigated the validity and transferability of results from laboratory measurements previously reported in the literature to more natural settings and behaviors. The third study analyzed the abnormalities of basic eye-movement parameters in schizophrenia patients in a natural environment and determined to what extent task demands influence the performance of

the participants and whether patients are able to overcome some impairments, which were reported in the laboratory, using the rich information provided in the real world. Along the same lines, the fourth study examined the alterations of eye-movement parameters during healthy aging and possible influences of the various sensory input sources in real-world situations, which might allow for compensatory mechanisms concerning certain deficits found in the laboratory. The fifth and last study focused on mobile eye-tracking as a technique in the daily clinical routine at the example of patients with typical and atypical Parkinson's disease. Here, I examined the usability and efficiency of eye-tracking as a potential tool for providing objective parameters for medical diagnosis to the physician.

Monocular visual localization during eye movements

Abstract

Eye movements induce visual spatial mislocalization. The neural basis of this perceptual phenomenon is as yet unknown: physiological, behavioral and theoretical studies have suggested various neural mechanisms, from displacement of visual receptive fields during eye movements to erroneously decoded eye position. Here we utilized the mislocalization of briefly presented stimuli during different types of monocular eye movements (i.e. fixation, saccades and smooth pursuit eye-movements) to induce a perceptual localization shift around and into the blind spot, a region of the retina that is physiologically blind due to the absence of photoreceptors. Our study confirmed previous findings on binocular mislocalization for monocular vision and showed that mislocalization induced by different types of eye movements is capable to shift the perceived location of targets to a position a subject should be blind for. The area for which each subject perceived the least amount of targets, forming a *perceptual blind spot,* shifted for each form of eye movement in a functionally characteristic manner. The distinctive shapes of the perceptual blind spots for each subject were basically preserved during eye movements as compared to fixation. Our findings imply a linear combination of two independent neural signals as the neural basis of localization: a visual map and an eye-position signal. Both signals might be combined at a rather late processing stage, in which visual space is already fully represented. This hypothesis predicts, at a neuronal level, visual receptive fields at identical retinal locations across eye movements and agrees well with previous studies suggesting the source of perceptual mislocalization during eye movements by an erroneous internal representation of eye-position.

Results & Discussion

The retinal architecture requires primates to move their eyes more often than their heart beats to acquire a high resolution image of the outside world. However, eye movements challenge visual perception (Bremmer & Krekelberg, 2003). They fall into different classes, foveating and reflexive. Among the first, saccades, i.e. high-speed ballistic movements, are the most frequent ones. A number of saccade-induced perceptual phenomena have been described over the last years, ranging from selective suppression of vision (Bremmer et al., 2009; Burr et al., 1994) to modulation of temporal (Knöll et al., 2013), numerical (Binda et al., 2012) and spatial perception (Honda, 1991; Ross et al., 2001). A second type of eye movement, suited to keep a moving visual object of interest within the fovea, is smooth pursuit (SPEMs). Just as for saccades and different from introspection, visual perception during SPEMs is not veridical. Modulatory effects range from enhanced chromatic sensitivity (Schütz et al., 2008) to shifts in spatial perception (Mateef et al., 1981; van Beers et al., 2001; Königs & Bremmer, 2010). The neural bases of most of these perceptual effects are barely understood. Concerning spatial mislocalization, various hypotheses have been put forward: from shifting visual receptive fields (Duhamel et al., 1992; Ross et al., 2001) to erroneously decoded eye positions signals (Morris et al., 2012; Dowiasch et al., in preparation (Remark: study two in this thesis)). Here we investigated the monocular localization performance of briefly flashed stimuli during three types of eye movements (i.e. fixation, saccades, SPEM) in 16 human participants. We presented the localization targets close to the blind spot, an area of the retina with no photoreceptors, to induce perceptual mislocalization into a region that is physically blind. Thereby we wanted to investigate if and if so how and at what processing stage retinal signals about the visual position of a stimulus on the retina and extraretinal signals representing the current eye-position and the ongoing eye-movement are combined to the perceived location of a target.

The first result of our study is the finding of a mislocalization of briefly flashed stimuli for monocular vision as previously described for binocular vision. In our study we could show a perceptual undershoot of localization targets during steady fixation with a mean of 1.62° ± 2.20°, significantly different from zero ($t(df=15)=-2.95$, $p=0.01$, t-test), which is in the same range as reported for binocular vision (Hill, 1972; Morgan, 1978; Kaminiarz et al., 2007). Saccades showed a bi-phasic error pattern of visual localization around the time of a saccade

(Figure 1). This finding, as well as the magnitude and time course of the perceived shift and compression (Lappe et al., 2000), is well in line with results from studies employing binocular eye movements performed in complete darkness without visual references (Honda, 1991). We found an average peak mislocalization of up to 1.55° in direction of the saccade 30 ms before the saccade was initiated and a mean peak localization error of up to 1.27° in the direction opposite to the saccade 50ms after the eyes began to move.

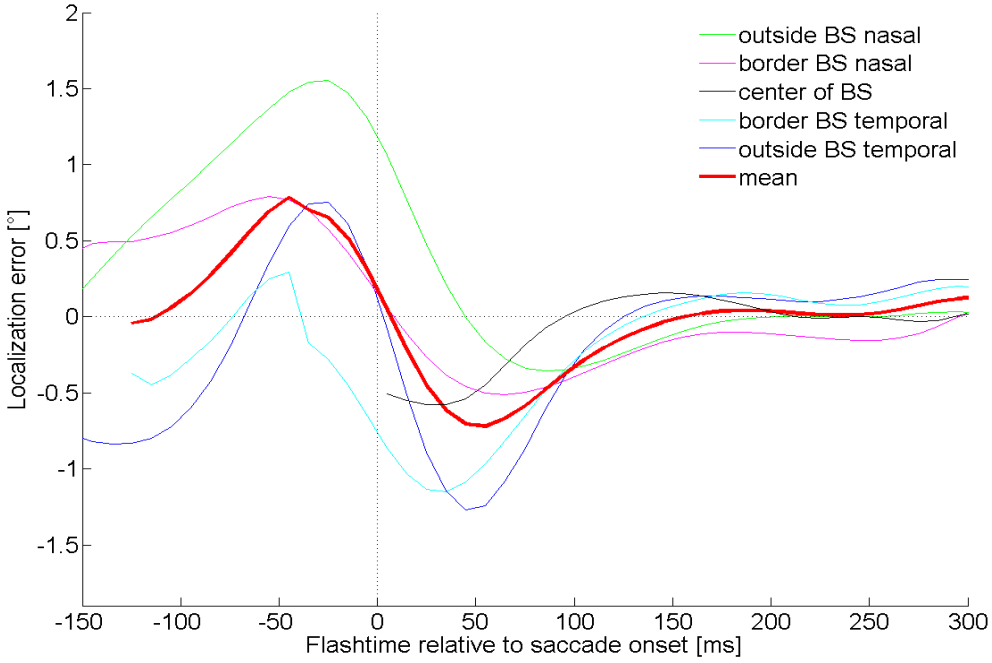

Figure 1: Normalized localization error around the time of a saccade
The localization error as a function of flash time relative to saccade onset of five flash locations (i.e. in the center, at the borders and beyond the blind spot on each side) averaged across all subjects and normalized such that the median mislocalization of each flashed position is aligned to zero. Positive localization errors indicate a mislocalization in direction of the saccade, negative values represent a shift in direction opposite to the saccade respectively. All five locations and the mean across all locations showed a clear bi-phasic error pattern of localization around the time of a saccade as reported previously for binocular vision.

During smooth pursuit eye-movements subjects mislocalized targets on average by 1.36° ± 1.12° in direction of the eye movement as compared to fixation, which was significantly different from zero ($t(df=10)=4.05$, $p = 0.002$, t-test). This mislocalization is in line with previous studies using binocular vision (Mateeff et al., 1981; van Beers et al. 2001; Königs & Bremmer, 2010). Depending on the particular magnitude of the mislocalization during the related eye movement, these effects lead to a perception of targets within the area of the physiological blind spot, a position the subjects are blind for due to the retinal architecture (Figure 2).

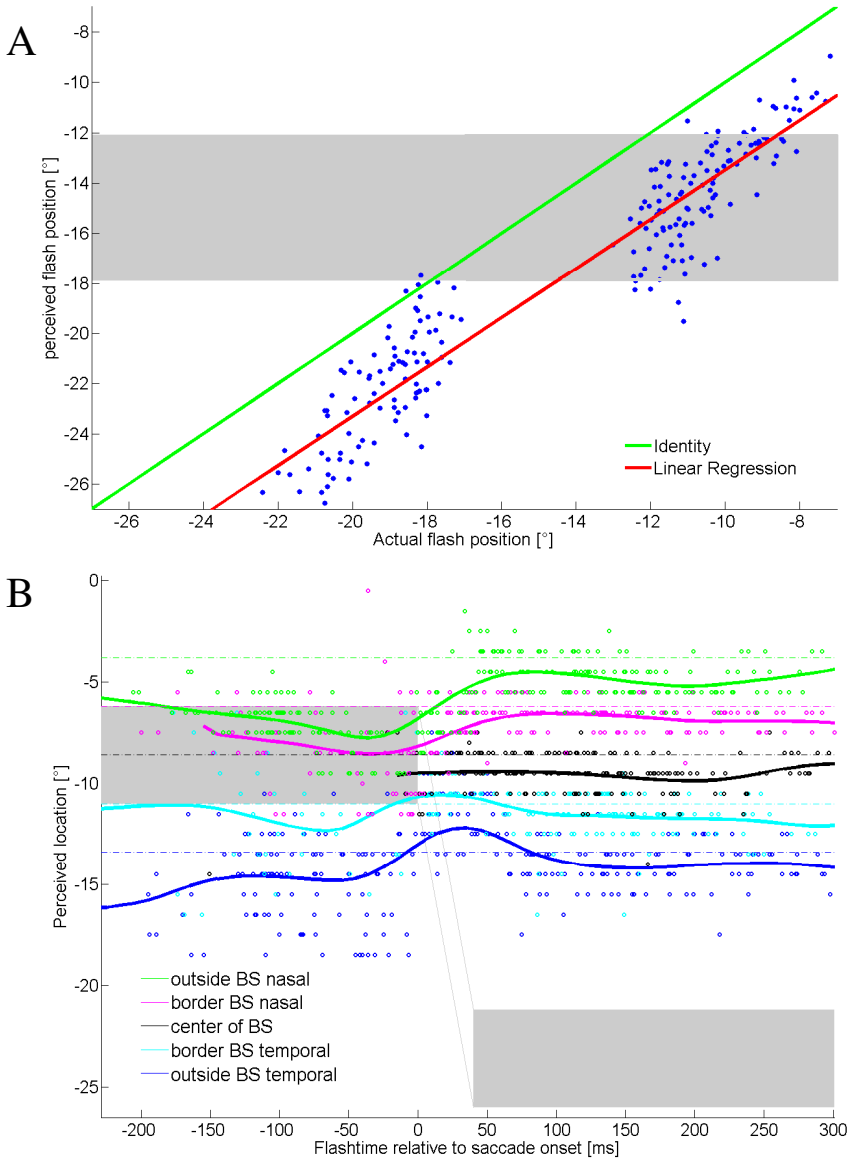

Figure 2: *Perception of flashed targets in the area of the blind spot due to mislocalization during eye movements. Each dot represents data from one trial. In A, the x and the y position of each dot indicate the real (x) and the perceived (y) horizontal eccentricity of the target. In B, the x-position indicates when relative to saccade onset a stimulus was presented. The y-position indicates the perceived horizontal position. Solid lines depict linear regression (A) or moving averages (window size = 75 ms, σ= 30 ms) (B) of localization performance*
A: Perceived flash position as a function of actual flash position during smooth pursuit eye-movements of a representative subject. The mean mislocalization of this subject was 3.40° resulting in a considerable amount of perceived stimuli shifted into the region of the blind spot (gray area).
B: Perceived flash location as a function of flash time relative to saccade onset of one representative subject. Dashed-dotted lines represent the actual location of the five localization targets. The perception of stimuli presented nasal of the blind spot (green and magenta curve) was shifted into the region of the blind spot (gray area) due to a mislocalization in direction of the saccade prior to saccade initiation.

This leads to the conclusion, that there is no special representation of the blind spot in the brain to register those locations as impossible and therefore dismiss them. Furthermore, it suggests that information about the location of a stimulus, which initially is correctly encoded, becomes distorted by a transformation of coordinates at an area where the visual space is already completely represented. Importantly, in the saccade paradigm even the location in the center of the blind spot, where stimuli could not be sensed before the eye started to move showed a significant localization error. Just as for the other four stimulus locations it showed the typical mislocalization pattern but this time beginning from the start of the saccade until 70ms after the eye started moving (all $p<0.05$, t-test). This shows that mislocalization occurs even for stimuli that had no visual representation before the eye movement was initiated. This mislocalization of briefly flashed stimuli during different types of eye movements could be due to a temporal misalignment between the retinal and extraretinal signals (Brenner et al., 2001), or a combination of the retinal target location and an erroneous internal representation of eye-position. This latter hypothesis was suggested by Morris and colleagues (2012) who showed that internal eye-position signals in four parietal areas of the rhesus macaque (i.e. MT, MST, LIP, VIP) are predictively computed and updated across saccadic eye-movements. Accordingly, such an eye-position signal would be readily available for a transformation of visual signals from a retinocentric to a craniocentric frame of reference. Yet, these internal eye-position signals showed comparably slow dynamics around the time of a saccade introducing an error, such that the internal eye-position signal already shifted 100 ms before a saccade was initiated and caught up with the actual eye-position only about 150 ms after the eye had reached its landing position. This time-course results in an erroneous internal representation of eye-position around the time of a saccade. A recent study by Dowiasch et al.(in preparation (Remark: study two in this thesis)) found a related mechanism of an erroneous internal eye-position signal which would allow perceptual mislocalization during optokinetic nystagmus (OKN) and a critical part of the mislocalization during SPEM. This theory is in line with the results of our current study suggesting that localization of a briefly flashed target is performed by combining the retinal location of the stimulus with a possibly inaccurate extraretinal eye-position signal. This combination eventually results in a misperception of the target location even into the blind spot region where localization is impossible.

During steady state eye-movements (i.e. fixation and smooth pursuit), the continuous presentation of targets around the area of the blind spot allowed us to compare the positions of the physiological optic disc to the area where each subject perceived the least amount of localization targets with regard to the frequency distribution of perceived target location. By employing the same algorithm used to compute the physiological blind spot (see methods) we were able to determine the dimensions of the region we name the *perceptual blind spot*. The size of the perceptual blind spot was smaller than the physiological blind spot for all subjects and eye movements by a mean of 1.17° ± 0.87° ($t(df=18)=-5.86$, $p = 1.49 * 10^{-5}$, t-test). A comparison of the centers of both blind spots showed a linear shift of the position of the perceptual blind spot compared to the position of the physiological blind spot in the exact amount of the mislocalization during each eye movement for every subject (Figure 3A). This effect occurred during both fixation and smooth pursuit eye-movements and only depended on the mislocalization induced by the particular eye movement. Despite the fact, that the perceptual blind spot was on average 0.76° ± 0.68° ($t(df=10)=3.71$, $p = 0.004$, t-test) bigger during pursuit than during fixation, the general shape of the perceptual blind spot did not differ much within each subject besides a shift of the local minimum. To evaluate this we computed the cross-correlation of the shape of the perceptual blind spot during fixation and during SPEM for each subject. Thus we obtained the shift magnitude representing the best overlap between the two perceptual blind spots during the different types of eye movements at the maximum of the cross-correlation (Figure 3B). This shift showed a significant correlation with the mean mislocalization of each subject ($r= 0.82$, $p = 0.002$; Pearson's linear correlation). Furthermore, our results showed rather large interindividual variability of the perceptual mislocalization during each eye movement. Yet, the position of the center and the general shape of the entire perceptual blind spot always shifted along with the individual mislocalization of each eye movement and participant. This is strong evidence for a shift of the entire representation of perceptual space along with the observed mislocalization pattern. Our results suggest that this might be caused by a linear combination of retinal location information and an extraretinal eye-position signal. This neural computation has to take place in an area in which information about the entire visual space is available.

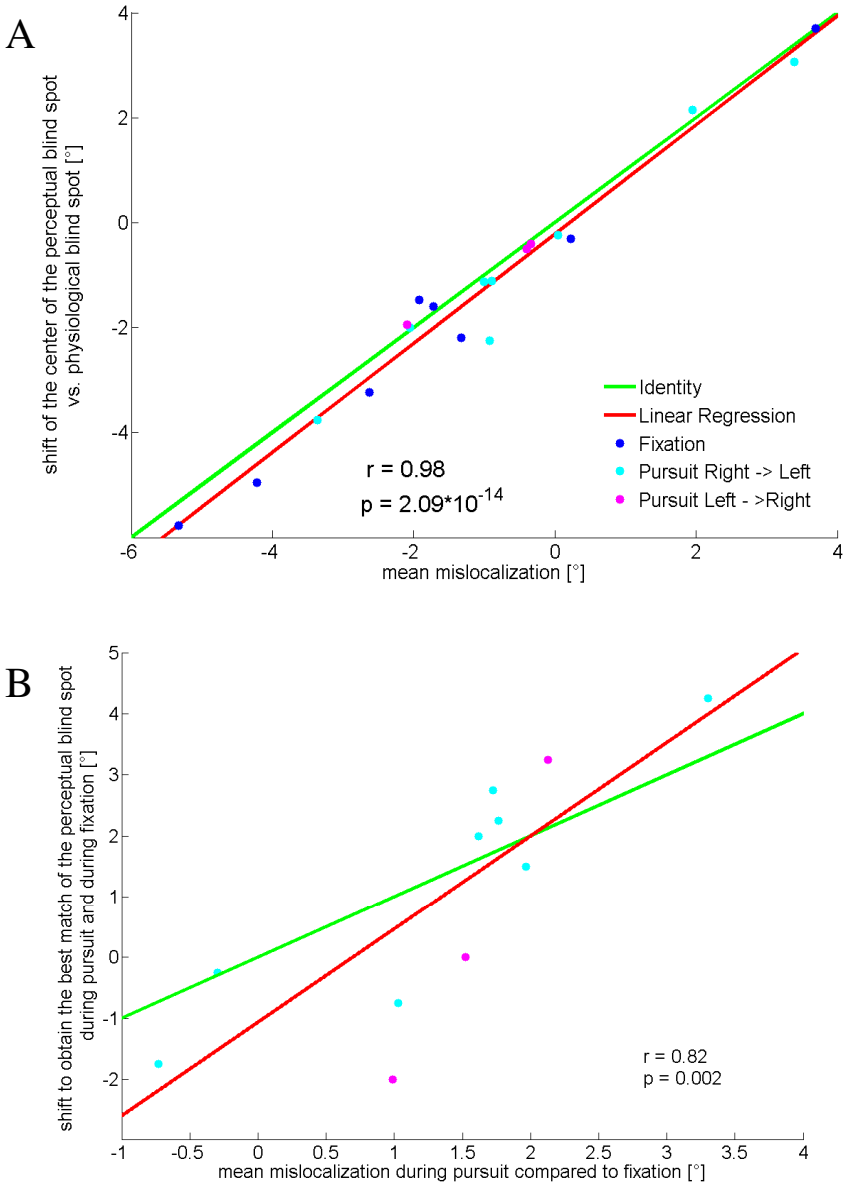

Figure 3: **Relationship of the physiological and the perceptual blind spot and the corresponding mislocalization during steady fixation and SPEM**
A: There is a strong linear relationship between the mean mislocalization and the shift of the position of the perceptual blind spot compared to the position of the physiological blind spot for each subject and eye movement. Negative values represent an underestimation of the target location or a mislocalization opposite to the pursuit direction, respectively.
B: Size of the shift of the perceptual blind spot during pursuit and fixation which maximized their cross-correlation as a function of mislocalization during pursuit as compared to mislocalization during fixation. Positive values represent a mislocalization in direction of pursuit.

Taken together our results suggest that the localization of briefly flashed stimuli results from a rather late linear combination of two independent neural signals, i.e., information about the retinal location of a stimulus and information about the current eye-position and the ongoing eye movement. Recent studies have shown, that an error in the internal eye-

position signal is capable to explain the well known mislocalization patterns during saccades (Morris et al., 2012) as well as smooth pursuit and optokinetic nystagmus (Dowiasch et al., in preparation (Remark: study two in this thesis)). The hypothesis of a linear combination of two independent signals predicts at a neuronal level visual receptive fields (RF) at identical retinal locations during different types of eye movements. Experimental evidence comes from a recent neurophysiological study on RF properties in macaque area MT, showing that the location of the receptive fields were not affected by slow eye-movements (Hartmann et al., 2011).

Experimental Procedures

We investigated the monocular localization performance for briefly visual stimuli flashed during steady fixation, saccades and smooth pursuit. Sixteen human subjects participated in the experiment, each performing eye movements with the left eye while the right eye was blindfolded by an eyepatch. All participants were measured during steady fixation. Eight subjects performed horizontal smooth pursuit, three of them in both directions (from left to right and vice versa) and eight subjects performed saccades. All participants had normal or corrected to normal vision and gave their written consent prior to the experiment. All measurements where performed in a dark and soundproofed room. Stimuli were projected by a video-projector running at 100Hz on a tangent screen (width: 1.60m, height: 1.20m, corresponding to 70°x50° of visual angle), 114 cm in front of the subjects. Head movements where restricted by a chin rest. Eye movements where recorded with an Eyelink II (SR-Research) at 500Hz. Stimuli were presented with Neurostim *(open source environment based on visual c++ and open GL)*. Subjects responded with a keyboard in front of them.

Paradigm

The experiment consisted of a fixation- and a pursuit-task or a fixation- and a saccade-task respectively, presented in separate sessions, as illustrated and described in Figure 4.

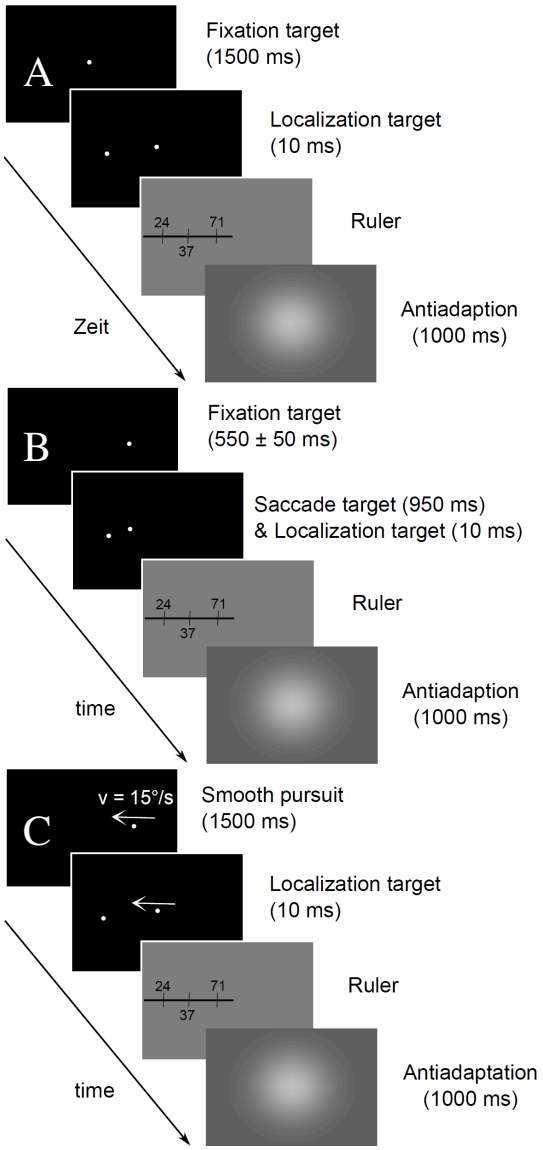

Figure 4: Schematic overview of the experimental paradigms for fixation (A), saccades (B) & smooth pursuit (C)

A: A fixation target was presented at the center of the screen for 1500 ms. Between 1100 – 1500 ms a localization target appeared for 10 ms at a random position between 7° - 22° left of straight ahead and 2° beneath the horizontal meridian. After the initial fixation target disappeared, subjects reported the perceived location of the flashed target with a ruler stimulus, followed by presentation of a gaussian luminance distribution for 1000 ms to prevent dark-adaptation.

B: After an initial fixation at 7.5° right of straight ahead for 500 – 600 ms, the target disappeared and a second target was presented at 7.5° left of straight ahead, being visible for 950 ms. The timing and position of the localization target was adjusted for each participant depending on his/her mean saccade latency and the location and size of his/her blind spot. Across trials, the target to be localized occurred from around 200 ms before until 300 ms after a saccade was initiated at one of five predefined locations clearly outside, at the boarders or directly in the center of the blind spot. After the saccade target went off, the ruler stimulus appeared followed by a gaussian luminance distribution to prevent dark-adaptation.

C: In the normal pursuit-task a dot was presented 12° right of straight ahead and started moving leftwards with a speed of 15°/s 500 ms after appearance. On a randomly chosen point in time between 1100-1500 ms after trial start the localization target was flashed for 10 ms at a random position between 7°-22° left of straight ahead (in the visual hemifield ahead of the pursuit target) and 2° beneath the horizontal meridian. The pursuit target disappeared 1500 ms after onset and a ruler stimulus became visible to allow subjects to report the perceived location of the flash. Three subjects additionally performed pursuit from left to right with the target starting 12° left of straight ahead. All other parameters were equal resulting in a presentation of the localization target in the visual hemifield the eye moves away from.

In general: A white dot (luminance: 22.1 cd/m², diameter: 0.5°), on a black background (luminance: < 0.1 cd/m²) was used for all paradigms as fixation and localization target. During steady fixation and pursuit, the localization target was flashed in a continuous area

adjusted to match the blind spot of each subject with a temporal jitter of 200 ms to prevent pursuit anticipation. In the saccade paradigm, the presentation time of the localization target was adjusted to the mean saccade latency of each subject to roughly cover stimulus presentation times in a range from 200 ms before until 300 ms after saccade initiation. Like in the other two paradigms, the position of the localization target was aligned to the dimensions of the blind spot measured for each participant during fixation in a way that one target was presented in the center, two targets at the computed nasal and temporal border and two targets well outside the blind spot, one each on the nasal and temporal side. In all paradigms a ruler stimulus was presented at the end of a trial to allow subjects to report the perceived localization of the target (see e.g. Kaminiarz et al., 2007). Briefly, the ruler consisted of vertical white lines with a distance of 0.5° on a grey background and a number alternating above and beneath each line randomly assigned for each trial. Subjects were asked to choose the line which corresponded best to the perceived position of the localization target and enter the associated number to the keyboard. If they had not perceived the flashed dot, subjects were told to enter “00”. After that an anti-adaptation screen with a gaussian luminance distribution appeared for 1000 ms to prevent complete dark adaptation.

Data Analysis

Data analysis was performed with Matlab2010b (The MathWorks Inc., Natick, USA). First, the results from the fixation paradigm were used to compute the dimensions of the physiological blind spot of each participant. After dismissing every trial in which a subject performed a saccade within 300 ms of the flash presentation, each trial was assigned to “1” if the localization target was seen or “0” if not. These trials were plotted as a function of the actual stimulus position and fitted by a moving average (σ = 1°, window-size 2.5°) using a step size of 0.2°. The locations for which the discrimination rate dropped to 50% were defined as the borders of the physiological blind spot. Assuming that the blind spot is symmetrical (Armaly, 1969), the center of the blind spot was determined midway between both borders. During steady fixation and pursuit we analyzed the perceived flash-position as a function of the actual flash-position taking into account the computed position of the blind spot for each subject. This allowed us to compute the amount of perceived stimuli within the area of the blind spot and the mean mislocalization during each eye movement. In the

saccade paradigm, the perceived location of the flash was analyzed as a function of time aligned to saccade onset to obtain the typical bi-phasic pattern of localization around the time of a saccade for each subject. By incorporating the area of the blind spot, one could identify stimuli perceived within the blind spot due to the mislocalization induced before the eye started moving.

Furthermore, during steady fixation and pursuit, we computed the size of the area in which the least amount of stimuli were perceived, which we call the *perceptual blind spot*. The borders were calculated by using the same algorithm as for the physiological blind spot to compute the moving average of the frequency distribution of the perceived target location. As the only difference, the borders of the perceptual blind spot were considered at the location where the relative frequency of the perceived target location was exactly half between its minimum and maximum. This analysis allowed us the compare the size and the position of the area in which stimuli could not be physically recognized (physiological blind spot) with the area in which each subject actually perceived the least amount of stimuli during a particular eye movement (perceptual blind spot), to investigate the impact of the respective eye movement on the perceptual representation of the visual field in general.

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Neural basis of spatial mislocalization during smooth eye-movements

Abstract

The dependence of neuronal discharge on the position of the eyes in the orbit is a functional characteristic of many visual cortical areas of the macaque. It has been suggested that these eye-position signals provide relevant information for a coordinate transformation of visual signals into a non-eye-centered frame of reference. This transformation could be an integral part for achieving visual perceptual stability across eye movements. Previous studies demonstrated close to veridical eye-position decoding during stable fixation as well as characteristic erroneous decoding across saccadic eye-movements. Here we aimed to decode eye-position during smooth-pursuit. We recorded neural activity in macaque area VIP during steady fixation, saccades and smooth-pursuit and investigated the temporal and spatial accuracy of eye-position as decoded from the neuronal discharges. Confirming previous results, during steady fixation the activity of the majority of neurons depended linearly on horizontal and vertical eye-position. The application of a previously introduced computational approach (isofrequency-decoding) allowed eye-position decoding with considerable accuracy. We applied the same decoder on the activity of the same neurons during smooth-pursuit. On average, the decoded signal was ahead of the current eye position. A model combining this constant lead of the decoded eye-position with a previously described attentional bias ahead of the pursuit target describes the asymmetric mislocalization pattern for briefly flashed stimuli during smooth-pursuit eye-movements as found in human behavioral studies.

Introduction

When an object of interest moves through our visual field we can track it with an eye movement in order to stabilize the object's image on the retina. The control of such smooth pursuit eye movements (SPEMs) relies on visual motion information ('retinal slip') (Ilg, 1997) as well as on efference-copy signals (Von Holst & Mittelstaedt, 1950; Thier & Ilg, 2005). These so-called extraretinal signals are ubiquitous in the visual cortical and sensorimotor system of the macaque. An influence of the position of the eyes in the orbit has been found in striate (Trotter and Celebrini, 1999), extrastriate (Galletti & Battaglini, 1989; Bremmer et al. 1997a; Bremmer, 2000), parietal (Andersen & Mountcastle, 1983; Bremmer et al., 1997b, 1999; Morris et al., 2012, 2013) and even premotor cortex (Boussaoud et al., 1998). The relationship between neural activity and eye position has been termed 'gain field' or 'eye-position field'. It has been suggested that gain fields are of critical importance for a stable perception of our environment by allowing for a coordinate transformation of visual signals from eye-centered to non-eye-centered spatial representations (Zipser & Andersen, 1988; Bremmer et al., 1998; Snyder et al., 1998; Boussaoud & Bremmer, 1999; Salinas & Abbott, 2003; Blohm et al., 2009; Blohm, 2012).

Eye-position decoding typically has been applied to the stationary case, i.e. the fixating eye. It was only recently that decoding has been introduced to the dynamic case (Morris et al., 2012, 2013; Xu et al., 2012). By applying population decoding approaches on data from saccades, Morris and colleagues (2013) could show that eye-position signals in four extrastriate and parietal areas of the macaque visual cortical system are precise on short time scales. Yet, eye-position decoding was not veridical in the temporal vicinity of saccades. Instead, the decoded eye-position was leading the real eye-position briefly before the onset of a saccade, but lagging at the end (Morris et al., 2012). This bi-phasic error pattern resembled the results from human psychophysical studies on the localization of perisaccadic visual stimuli. The authors therefore suggested that the erroneous eye-position signal could be the neural basis of the observed behavioral phenomenon.

Psychophysical experiments in humans have shown a systematic localization error also for stimuli flashed during smooth eye-movements: pursuit onset (Blanke et al., 2010), steady-state pursuit (Mateef et al., 1981; van Beers et al., 2001; Königs & Bremmer, 2010),

anticipatory pursuit (Blohm, et al., 2003) and optokinetic nystagm, OKN (Kaminiarz et al., 2007). During OKN, stimulus locations across the whole visual field are perceptually shifted in the direction of its slow phase. During pursuit, however, spatial localization is asymmetric. Mislocalization is observed only in the visual hemifield ahead of the pursuit target. The neural bases of these perceptual phenomena are as yet unclear. Given the above described results on decoding of eye-position across saccades, we hypothesized that continuous eye-position decoding across smooth-pursuit eye-movements is possible but likely not veridical. We re-analyzed neural activity from macaque area VIP which had previously been recorded while monkeys performed smooth pursuit eye-movements in otherwise darkness (Schlack et al., 2003). By employing a computational approach (isofrequency decoding: Boussaoud & Bremmer, 1999) we found that decoded eye-position was not veridical but rather ahead of the actual eye position. While spatial attention during OKN is equally distributed across space, smooth pursuit induces an attention-field which is centered ahead of the pursuit target (Khan et al., 2010). Attention is known to induce a shift of visual receptive fields towards its center (Ben Hamed et al., 2002; Womelsdorf et al., 2006), leading to a perceptual expansion of space away from its center (Wardak et al., 2011). We hypothesize that a model, combining two independent signal sources, i.e. an erroneous eye-position signal and a spatial signal derived from a visual map distorted by attention, can explain the error pattern of localization of brief visual stimuli during smooth eye movements.

Methods

The current study is an extended computational analysis of neural and behavioral data reported before (Schlack et al., 2003). Accordingly, the procedures described here focus on the analytical treatment of the data and provide only the most relevant specifics of the behavioral and electrophysiological procedures. Full details of experimental methods are provided in our previous report (Schlack et al., 2003).

Animal preparation

Experimental and surgical preparation followed standard procedures. In brief, two monkeys were prepared for recordings under general anesthesia and under sterile surgical conditions. Each animal was implanted with a device for holding the head. Based on structural MRI scans a recording chamber for microelectrode penetrations through the intact dura was placed in a frontal plane at an angle of 45° with respect to the vertical for recordings in area VIP. Additionally, scleral search coils were implanted to monitor eye position (Judge et al., 1980). During the experiment, the animal sat in a primate chair with the head restrained, facing a translucent screen and performing oculomotor tasks for liquid reward. All procedures were in accordance with published guidelines on the use of animals in research (European Council Directive 86/609/EEC) and were approved by the regional ethics committee.

Behavioral paradigm

Oculomotor targets (red LEDs, diameter: 0.8°, luminance: 0.4 cd/m²) were back-projected onto a translucent screen (size: 90°x90°) 48 cm in front of the monkey. All experiments were performed in darkness (luminance < 0.01 cd/m²). To prevent dark adaptation, lights were briefly switched on prior to a new set of trials.

In the saccade paradigm a central fixation target was presented for 1000ms, followed by a 10° step, pseudo-randomly chosen into one of four directions (left, right, up, and down). The animals' task was to perform a saccade to the target location within 500ms and keep fixation until the end of the trial (2.5 s). Smooth pursuit eye movements were induced by a Rashbass-'step-ramp-paradigm' (Rashbass, 1961). Here, the target moved in pseudo-randomized order at 10°/s into one of four directions (left, right, up, and down). After initial

presentation of a central fixation target (800ms) the target was shifted by 10° in the direction opposite to the following smooth pursuit direction and started to move instantaneously for 1500ms. Accordingly, each trial had a total duration of 2.3 seconds.
Binocular eye movements were continuously recorded at 200 Hz in the pursuit task and at 500 Hz in the saccade task. Spikes were detected on-line and spike-times were stored for offline analysis with 1ms resolution.

Data analysis

Eye-movement data and neuronal activity were analyzed with MATLAB 2012a (The MathWorks Inc., Natick, USA). Saccade onset was determined by a velocity criterion with a threshold of 80°/s in a time window of 0 – 400ms after target displacement. Spike times were converted to a spike density function using a Gaussian smoothing window of 90ms width (σ = 30ms). Eye-movement and neural data were aligned to saccade onset.

Isofrequency decoding

Neural activity as obtained during steady fixation in the saccade paradigm was used to determine a cell's eye-position field. Many previous studies have shown the eye-position effect to be linear along horizontal and vertical eye-position, also in area VIP (Bremmer et al., 1999). Accordingly, we fitted two-dimensional linear regression functions to the neuronal discharges (Figure 1). A regression plane represents the tuning of a cell for eye position: the gradient represents the direction of the steepest increase of activity with eye-position, the intercept determines the average discharge of the neuron. Regression planes were fitted to the average neural discharges obtained long before (pre-saccadic: -700ms to -200ms) and long after saccade onset (post-saccadic: +300ms to +900ms). During these epochs, the eyes were constantly positioned either at the screen center (pre-saccadic. [x, y] = [0°,0°]) or at one of the four eccentric fixation locations (post-saccadic. [x, y] = [+/-10°, 0°], [0°, +/-10°]). By choosing these analysis windows we excluded interference of eye-position dependent neuronal discharges with saccade planning and/or execution. For each cell the values of the regression plane as determined from the saccade paradigm were applied to neural activity recorded in the pursuit paradigm. This allowed us to decode eye-position continuously across the SPEM by employing an isofrequency decoding regime (Boussaoud & Bremmer, 1999). This population decoder is based on the planar tuning of the eye-position signals. For

a given eye position a neuron fires at a specific frequency. Yet, due to the planar tuning, this discharge occurs not only for one single eye position, but for a whole range of eye positions. In a mathematical sense, the discharge occurs for an infinite number of eye positions, all located along a straight line perpendicular to the gradient of the regression plane, the so-called 'isofrequency line'. Accordingly, discharges from a single neuron are not sufficient to decode eye position unequivocally. Considering discharges from a second neuron, however, theoretically would be sufficient, given that second neuron would have a different tuning for eye position. In such case, also for this second neuron an isofrequency line on its regression plane could be found. This line, however, would be differently oriented in the 2-D eye-position space. The only point located simultaneously on both isofrequency lines is the point of intersection (PI) of these lines, which represents the current eye position.

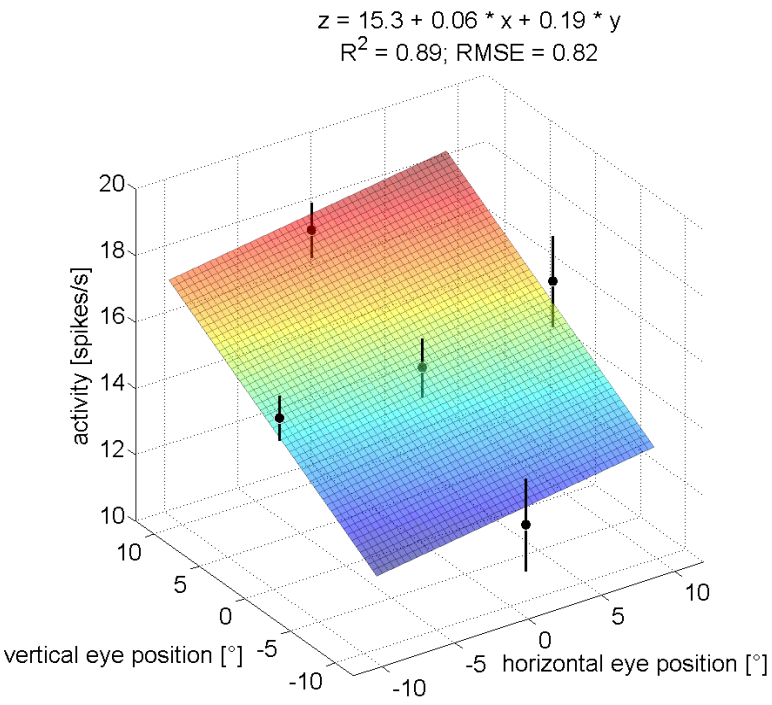

Figure 1: Eye-position tuning of one representative example neuron during the saccade paradigm
The color-coded plane represents the two-dimensional linear regression of the neuronal activity as a function of five different eye-positions averaged over a pre- and postsaccadic time epoch from -700 ms to -200 ms and 300 ms to 900 ms around saccade onset (black dots).The black vertical lines show the standard deviation of the mean at each data point. The regression equation and its goodness of fit parameters are given above the figure.

This scenario reflects the ideal case of a perfect linear fit of a 2-D regression plane to the neuronal discharges and constant discharges over time. Due to temporal fluctuations of the neural signal and due to imperfect 2-D linear fits, the PI obtained from two single neurons is typically only a coarse measure of the current eye position. Hence, the isofrequency regime considers the PIs obtained from a whole population of neurons: for n neurons, these are

(n*(n+1)/2) PIs. The decoded eye-position is computed as the median of the distribution of all PIs.

Attention and localization during smooth pursuit

Smooth pursuit induces an attentional field which is broadly ahead of pursuit (Kahn et al., 2010). Attention induces (or is based on) a shift of visual receptive fields towards the attended location (Ben Hamed et al., 2002; Womelsdorf et al., 2006). This shift of visual RFs in turn leads to a perceptual expansion of visual space (Wardak et al., 2011). We modelled such an expansion based on the structure of the attentional field during smooth pursuit as given by Khan et al. (2010), i.e. their equation for saccade reaction times, given in the legend of their Figure 8. Boundary conditions of our model of perceptual expansion of space due to attention resulted from behavioral data in humans showing (i) almost no mislocalization during SPEM in the visual hemifield behind the pursuit target and (ii) smaller localization error in the directions perpendicular to the pursuit direction (van Beers et al., 2001; Königs & Bremmer, 2010). In our model, overall localization error then results from superimposing two signals: (i) decoded eye position and (ii) a visual map, distorted by attention.

Statistical analysis

To statistically evaluate the relative error of the decoded eye-position signal compared to the actual eye-position we performed a bootstrap analysis (Efron, 1979) of the mean relative error within each particular time window with 100.000 iterations. This analysis provided confidence intervals, which were used to asses significance levels.

Results

This study is based on recordings from 180 neurons in area VIP of two macaque monkeys. The discharges related to smooth pursuit eye-movements haven been described in detail before (Schlack et al., 2003). Here, we focused on the decoding of eye-position signals from these neuronal discharges. In addition to smooth pursuit eye movements, monkeys performed in separate sets of trials visually guided saccades. Discharges during continuous, steady fixation long before or long after a saccade were used to determine a neuron's eye-position field. An example for such an eye-position dependent modulation of spontaneous

activity during active fixation is shown in Figure 1. For this neuron strongest activity was observed for fixation up and to the right (redish colors), while lowest discharges were observed for fixation left and down. The 2-D regression plane could be fitted significantly to the cell's discharges. This result confirms data from previous studies (Bremmer et al., 1999; Morris et al., 2012). During steady fixation, a given eye position results in a certain neuronal discharge. This discharge, however, does not occur only for a single eye position. Instead, it occurs, in a mathematical sense, for an infinite number of eye positions, all located along a straight line. For the example neuron in Figure 1, such lines are represented by identical color values on the 2-D regression plane. As shown previously (Boussaoud & Bremmer, 1999), real eye-position should be given by the median of the pairwise points of intersection (PIs) of a population of cells. Indeed, based on the discharges of the whole population of VIP neurons, decoded eye-positions during steady fixation were close to the real eye-positions (Figure 2). For the five positions tested, average absolute error of eye position decoding was only 1.83 degrees.

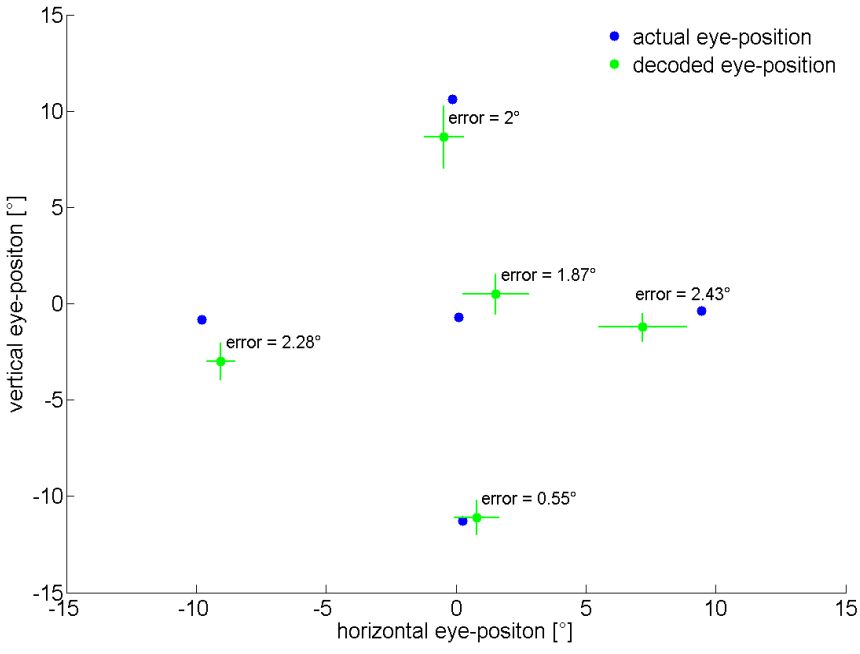

Figure 2: Accuracy of the eye-position signal in area VIP during steady fixation
Actually measured eye-position (blue dots) compared to median decoded eye-position (green dots) for each position during steady fixation in the saccade paradigm. Error bars represent the corresponding standard deviations. Absolute error of the decoded eye-position is given next to each location.

The decoded eye-positions show a good match for all five actual eye-positions (mean absolute error = 1.83°). This indicates an accurate internal eye-position signal in area VIP.

Continuous decoding of eye position

In a second step we analyzed the accuracy of the decoded eye position outside steady fixation, i.e., across the saccades. Confirming previous results (Morris et al., 2012, 2013), our analysis revealed a bi-phasic perisaccadic error pattern (Figure 3). A subtle increase of error in direction of the upcoming saccade was followed by a large error in direction opposite to the saccade. During steady fixation prior to the saccade, i.e. in a time window from t = 400ms to t = 200ms before saccade onset, the mean error was ε = -0.06°, which was not significantly different from zero (95% confidence Interval = [-0.33 0.22], bootstrapped with 100000 iterations; Figure 3, left inset). An analogue result was obtained for steady fixation well after the saccade, i.e. from t = 300ms to 500ms after the onset of the saccade. Here, the mean error ε = 0.02° again was not significantly different from zero (95% confidence Interval = [-0.25 0.29], bootstrapped with 100000 iterations; Figure 3, right inset).

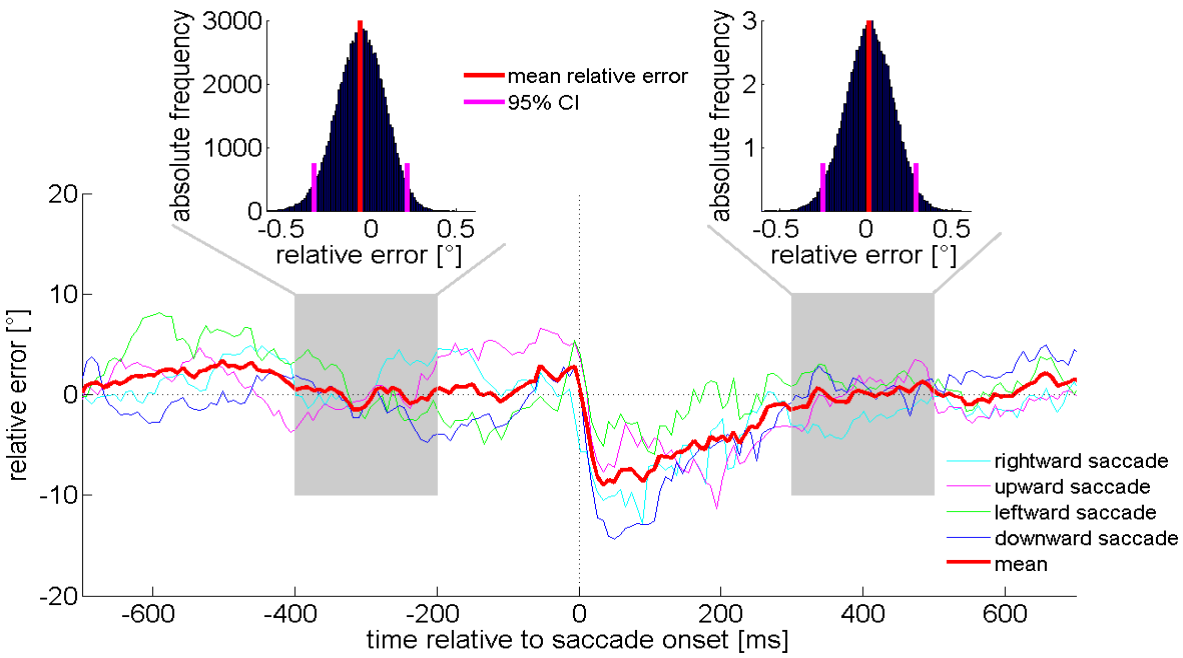

Figure 3: Relative error of the decoded eye position as a function of time in the saccade paradigm

A: The mean relative error of the decoded eye-position around zero degree pre- and post-saccadicly indicates an accurate representation of eye position during steady fixation. The mean relative error increased after initiation of the saccade in direction opposite to it, represented by a negative relative error. Bootstrapped distribution of the mean relative error and the corresponding 95% confidence interval during steady fixation prior, i.e. from t = -400ms to t = -200ms (left gray area) and after, i.e. from t = 300ms to t = 500ms (right gray area) the saccade. The relative error in both time windows did not differ significantly from zero.

In a third step of our analysis, we aimed to decode eye-position during smooth pursuit. Eye-movements had been recorded in a classical Rashbass-paradigm (Rashbass, 1961). After initial fixation, the target stepped in pseudo-randomized order into one of four directions (right, up, left, or down) and instantaneously started to move in the opposite direction. Critically, for decoding, we applied the regression plane values as obtained from the saccade paradigm to the neuronal discharges recorded during smooth pursuit. In other words: the neural samples, from which the fit parameters were obtained, were different from the samples, to which the decoding algorithm was applied.

Well before pursuit onset, i.e. in a temporal window from t =400ms to t=200ms before onset of the initial catch-up saccade, the mean relative error of the decoded eye-position was minimal (ε = -0.05°) and not significantly different from zero (95% confidence Interval = [-0.31 0.20], bootstrapped with 100000 iterations; Figure 4, left inset). After a minimal negative blip, it increased markedly in direction of the upcoming pursuit around the time of the catch-up saccade (Figure 4). Since the initial saccade was in opposite direction to the pursuit, this effect equals the pattern observed in the saccade paradigm. After the catch-up saccade and its related decoding error, the relative error decreased to an almost constant level. During steady state pursuit, i.e., in the time window from t=300 to t=1000 ms after saccade onset, the mean error was 1.37°. A positive value indicates a lead of the decoded eye-position in direction of the pursuit as compared to the actual eye-position. This lead of decoded eye-position was statistically significant (99.9% confidence Interval = [1.03 1.69], bootstrapped with 100000 iterations; Figure 4, right inset).

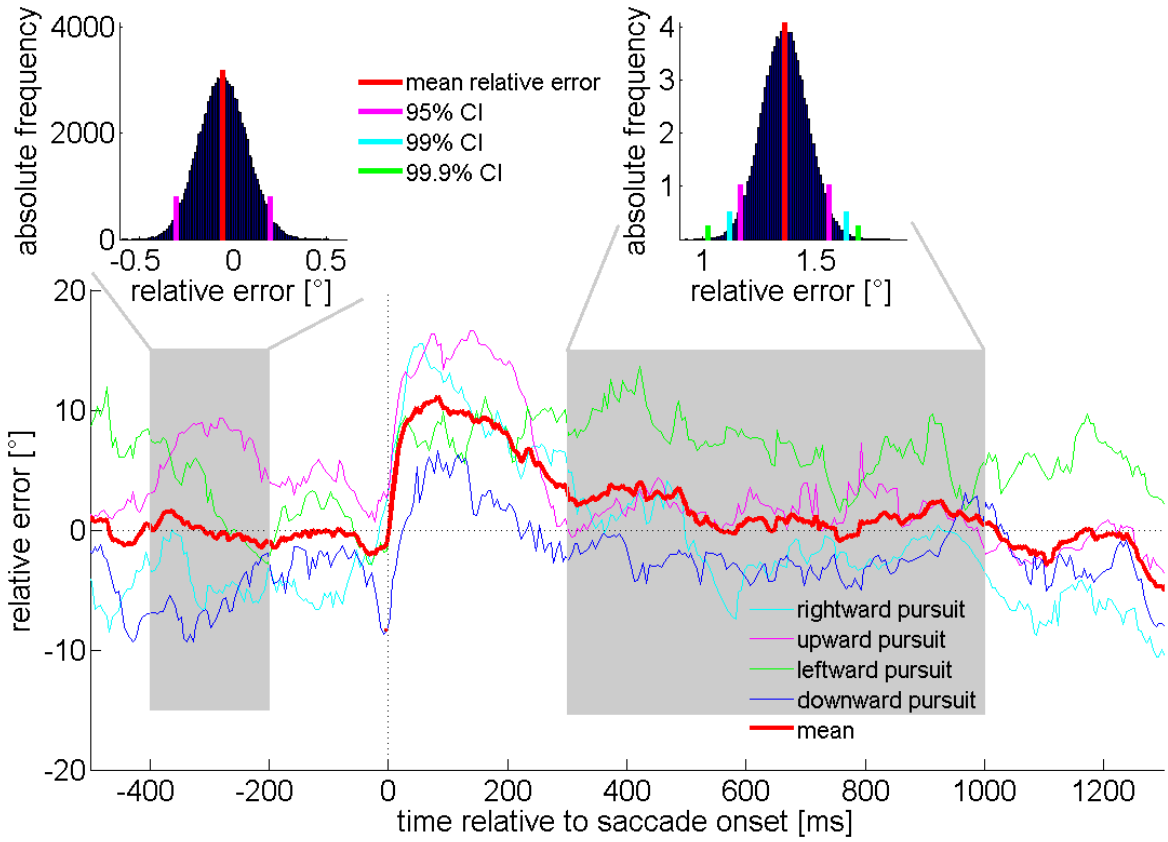

Figure 4: Relative error of the decoded eye position as a function of time in the pursuit paradigm

As for the saccade paradigm, the relative error of the decoded eye-position was largest around the time of the saccade due to a shift of the decoded eye-position in the direction opposite to the saccade, i.e. the direction of the upcoming pursuit. During steady state pursuit (between 300 – 1000 ms) the decoded eye-position showed a lead ahead of the actual eye-position indicated by the positive mean relative error of 1.4°*. Bootstrapped distribution of the mean relative error and the 95% corresponding confidence interval during steady fixation prior to the saccade, i.e. from t = -400ms to t = -200ms (left gray area) and during steady state pursuit, i.e. from t = 300ms to t = 1000ms (right gray area) after saccade onset. The mean relative error in the time window before the saccade did not differ significantly from zero, whereas the mean relative error during steady state pursuit was significantly greater than zero (99.9% confidence Interval = [1.03 1.69], bootstrapped with 100000 iterations).*

Decoded eye-position and attention

Given that a functional equivalent of macaque area VIP has been identified in human parietal cortex (Bremmer et al., 2001), erroneous eye position signals most likely also exist in the human visual cortical system. Accordingly, if spatial localization would rely among other signals on an estimate of eye position, a constant lead of decoded eye position would suggest a shift of perceived spatial locations in the direction of pursuit across the whole

visual field. Such a constant perceptual shift has been described for the slow phases of optokinetic look nystagmus (Kaminiarz et al., 2007). During pursuit, however, mislocalization is only found in the visual hemifield ahead of the fovea. In order to explain this asymmetry in spatial localization during SPEM, we suggest an additional mechanism to act in concert with the erroneous eye position signal: attention. Attention has been shown to lead to a perceptual distortion of space, i.e. an expansion of perceived locations away from the focus of attention (Wardak et al., 2011). Khan and colleagues (2010) have mapped the attentional field during pursuit and found attention centered broadly ahead of pursuit. We hence modeled the effect of attention on spatial localization by transforming the attentional map as given by Khan et al. (2010) into a (mis-)localization map:

(1) $L_{attention} = -65 * (-0.0848 + 0.065/(1 + \exp(0.328 * (x - 4.24))) + 0.05 * \exp(-((x - 4.734)^2 + (y -0.081)^2)/5.8032))$

In this equation (1), scaling factors were adjusted to meet the boundary condition of localization, i.e. only a marginal error in the hemifield behind the fovea. According to our hypothesis, localization during smooth pursuit should be given by a superposition of the erroneous eye position signal and the spatial map, which is distorted by attention:

(2) $L = L_{eye.pos.} + L_{attention}$

The resulting 2-D error pattern for localizing stimuli during smooth pursuit is shown in Figure 5. Horizontal localization error starts to build up at the vertical meridian. Vertical localization error is directed away from the focus of attention. This error pattern is almost identical to behaviorally data observed in humans (van Beers et al., 2001; Königs & Bremmer, 2010).

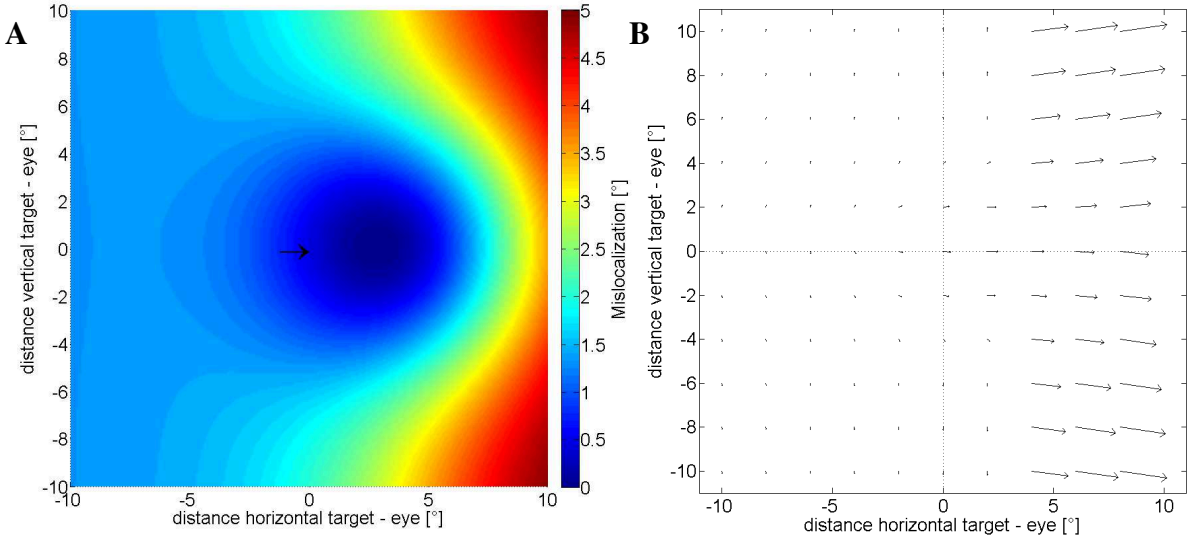

Figure 5: Modeled mislocalization during SPEM

A: The attention map found by Kahn et al. (2010) was transferred to represent spatial perception during smooth pursuit. As shown before, focused attention induces perceptual shifts away from the focus. In order to meet boundary conditions, the first two constant scaling factors of the 2D sigmoid and superimposed Gaussian fit function found by Kahn et al. (2010) were adjusted:

$z = -65 * (-0.0848 + 0.065/(1 + \exp(0.328 * (x - 4.24))) + 0.05 * \exp(-((x - 4.734)^2 + (y - 0.081)^2)/5.803^2))$. *The arrow illustrates the direction of pursuit with the head marking the location of the pursuit target.*

B: Cumulative mislocalization from the combination of attentional effects and a constant lead of the decoded eye-position signal of about 1.4° as found in our study. Both sources of mislocalization add up in the visual hemi-field ahead of the pursuit target and almost neutralize each other in the hemi-field behind the eye. The resulting figure closely resembles the behaviorally measured asymmetric mislocalization pattern typically observed during smooth pursuit eye-movements (van Beers et al., 2001; Bremmer & Königs, 2010).

Discussion

Efference copy vs. proprioception

Over the last three decades, numerous studies have shown that neurons in many visual cortical areas of the macaque carry an eye-position signal (e.g. Andersen and Mountcastle, 1983; Galletti & Battaglini, 1989; Bremmer et al., 1997a, b; Trotter and Celebrini, 1999; Bremmer, 2000), among them also area VIP (Duhamel et al., 1997; Bremmer et al., 1999; Morris et al., 2012, 2013). A number of different approaches have shown that the functional characteristics of these modulatory influences of eye position on neuronal discharge are suited to decode eye position from the activity of a population of neurons within each of

these areas: a back-propagation network (Andersen & Mountcastle, 1983), splitting a population into tow sub-populations with opposite tuning properties (Bremmer et al., 1998), an isofrequency decoding (Boussaoud & Bremmer, 1999), as well as a maximum likelihood approach (Morris et al., 2012, 2013).

Eye-position signals have also been documented for neurons in primary somatosensory cortex (Wang et al., 2007; Xu et al., 2011). Based on this finding, it was suggested that eye position signals result from proprioception rather than from an efference copy or from corollary discharge. In line with this hypothesis, it was shown that the strength of visual responses of a number of neurons from area LIP visually stimulated briefly after the end of a saccade was more compatible with pre-saccadic rather than post-saccadic eye positions (Xu et al., 2012). These findings are in contrast to results from two other recent studies (Morris et al., 2012, 2013). Here, Morris and colleagues tested the time course of the pure eye-position signals without any further visual stimulation in four different cortical areas of the macaque dorsal visual pathway: areas MT, MST, LIP, and VIP. The authors unequivocally showed that eye position as decoded from population activity within each of these areas started to change prior to saccade onset. Such a predictive change cannot be based on proprioception but rather would be indicative of an efference copy or corollary discharge signal. Our findings on decoded eye position leading the actual eye position during smooth pursuit are in agreement with the results from Morris and colleagues on saccades.

Continuous decoding of eye position

The result on the accuracy of decoded eye-position during steady fixation in our study was in line with those of previous studies on dorsal visual areas (Boussaoud & Bremmer, 1999; Morris et al. 2013). To decode the eye position during smooth-pursuit eye movements, we used the 2-D linear tuning of each cell as computed from the saccade paradigm and applied it to the neuronal discharges as recorded during SPEM. The error of the decoded eye-position during the initial fixation and the saccade to the pursuit target was in the same range and direction as in the saccade paradigm.

In line with previous studies, our data show that eye-position signals in area VIP are accurate and sufficiently fast to represent the actual eye-position not only during steady fixation, but also during ongoing eye-movements. Hence, they provide viable information for a coordinate transformation of visual signals from an eye-centered to a head-centered frame

of reference at the population level. Such a transformation is thought to be necessary not only for a stable perception of our environment (Zipser & Andersen, 1988; Salinas & Abbott, 2003; Bremmer, 2005), but also for the computation of pursuit motor commands in the correct reference frame (Blohm and Lefèvre, 2010; Murdison et al., 2014). It remains to be determined, if explicit head-centered representations at the single cell level, which have been shown for area VIP during steady fixation (Duhamel et al., 1997; Avillac et al., 2005; Schlack et al., 2005), can also be found across eye movements.

During steady state pursuit, the relative error of the decoded eye-position was positive. Such a positive error indicates that the internal representation of eye-position was slightly ahead of the actual eye-position. The finding of a lead of the decoded eye-position in relation to the actual eye-position could explain, at least in part, the behaviorally observed mislocalization of briefly flashed stimuli during SPEM (Mateeff et al., 1981; van Beers et al. 2001; Königs & Bremmer, 2010) or related smooth eye movements like the slow phase of optokinetic nystagmus (Kaminiarz et al., 2007): if the erroneously decoded eye position would be combined with information about the location of a visual stimulus on the retina, it could induce the above mentioned mislocalization. Similarly, a possible neural substrate of the mislocalization during saccades had been identified (Morris et al., 2012).

Indeed, the mean relative error of about 1.4° in our current study greatly matches the mean localization error reported during the slow-phase of look-nystagmus (Kaminiarz et al., 2007; Tozzi et al., 2007). In these experiments, visual stimuli were presented during ongoing OKN. When stimulus presentation fell in a slow phase of the OKN, stimuli were mislocalized in the direction of the eye movements. Stimuli, which were presented shortly before, during or after a fast-phase of the OKN were mislocalized according to a saccade-like error pattern. These results were very different from results during stare-nystagmus or during Optokinetic Afternystagmus (OKAN), which can be induced by prolonged optokinetic stimulation. In such case, mislocalization during the slow phase was not in the direction of the eye movements, but directed away from the fovea, resulting in a perceptual expansion of space (Kaminiarz et al., 2008). Interestingly, only SPEM and look-nystagmus are associated with very similar cortical activation patterns in motion sensitive and eye-movement areas (Konen et al., 2005), which is not the case for stare-nystagmus and OKAN. These results suggest that visual localization during eye movements, which are under cortical control, relies (at least in part) on decoded eye-position signals.

Decoded eye-position and attention

Different from look-nystagmus, however, mislocalization during smooth pursuit is asymmetric with respect to an eye-centered visual field: it is found almost exclusively in the visual hemi-field ahead of the pursuit target (or the fovea) (van Beers et al., 2001; Königs & Bremmer, 2010). There it increases from about 2° for stimuli close to the fovea to a maximum value of up to 5° for stimuli presented further away from the fovea. This suggests an additional signal contributing to the mislocalization during SPEM in addition to the erroneously decoded eye position.

Visual receptive fields have been shown to shift towards the location where attention is allocated (Ben Hamed et al., 2001; Womelsdorf et al., 2006). If the spotlight of attention coincides with the fovea, the receptive fields shift towards the fovea. According to a labeled line coding, this centripetal shift must result in a centrifugal shift of perceptual localization with respect to the fovea. Such a centrifugal shift away from the focus of attention has recently been demonstrated in behavioral experiments in humans (Wardak et al., 2011). During smooth pursuit, however, attention is not where the fovea is. Instead, a study of Khan et al. (2010) found that attention during SPEM is allocated broadly ahead of the pursuit target. By mapping response latencies to visual stimuli presented around the pursuit target, a peak of attention was found at about 4° ahead of the pursuit target. Accordingly, this spatial attention most likely induces a distortion of perceptual space with perceived locations directed away from the center (or focus) of attention. Figure 5A shows the function of the attentional field during SPEM found by Khan et al. (2010) converted to represent mislocalization under the assumption that the location with the highest attention shows the least mislocalization. This attentional landscape can be considered a potential field implying a centrifugal force always directed away from its center. We suggest that this distorted representation of perceptual space is superimposed onto the erroneously decoded eye-position signal. The combination of a spatial map, distorted by attention, and a constant lead of the decoded eye-position would add up to a joint localization map.

In this map, the effects of attention and decoded eye-position add to each other in the visual hemifield ahead of the focus of attention, but antagonize each other in the hemi-field behind the fovea (Figure 5B). The resulting error map very closely resembles the asymmetric localization error during smooth pursuit as found in behavioral experiments in humans (van Beers et al., 2001; Königs & Bremmer, 2010).

Without an attentional contribution only the constant lead of the decoded eye-position would induce a uniform mislocalization pattern across the visual field. Indeed, such an error pattern has been shown for the slow phase of look-OKN (Kaminiarz et al., 2007). Accordingly, our data suggest that it should be possible to decode eye-position from neural activity in macaque area VIP (and most likely further visual cortical areas) during the slow phases of look-nystagmus. Most likely, this decoded signal would not be veridical but rather show a lead with respect to real eye-position.

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ORIGINAL PAPER

Eye movements of patients with schizophrenia in a natural environment

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Abstract Alterations of eye movements in schizophrenia patients have been widely described for laboratory settings. For example, gain during smooth tracking is reduced, and fixation patterns differ between patients and healthy controls. The question remains, whether such results are related to the specifics of the experimental environment, or whether they transfer to natural settings. Twenty ICD-10 diagnosed schizophrenia patients and 20 healthy age-matched controls participated in the study, each performing four different oculomotor tasks corresponding to natural everyday behavior in an indoor environment: (I) fixating stationary targets, (II) sitting in a hallway with free gaze, (III) walking down the hallway, and (IV) visually tracking a target on the floor while walking straight-ahead. In all conditions, eye movements were continuously recorded binocularly by a mobile lightweight eye tracker (EyeSeeCam). When patients looked at predefined targets, they showed more fixations with reduced durations than controls. The opposite was true when participants were sitting in a hallway with free gaze. During visual tracking, patients showed a significantly greater root-mean-square error (representing the mean deviation from optimal) of retinal target velocity. Different from previous results on smooth-pursuit eye movements obtained in laboratory settings, no such difference was found for velocity gain. Taken together, we have identified significant differences in fundamental oculomotor parameters between schizophrenia patients and healthy controls during natural behavior in a real environment. Moreover, our data provide evidence that in natural settings, patients overcome some impairments, which might be present only in laboratory studies, by as of now unknown compensatory mechanisms or strategies.

Keywords Eye movements · Real-world gaze · Schizophrenia · Natural environment · Self-motion

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Introduction

Eye movements in schizophrenia patients have been a topic of research for more than a century [1]. A large number of different eye-movement abnormalities have been described. Examples include decreased smooth-pursuit gain [2–4], increased anti-saccade error rates and latencies [5], changes in saccade dynamics [6, 7], or different fixation patterns when viewing static pictures [8, 9].

Except one recently published study that found differences in scan-path patterns in unfamiliar environments between schizophrenia patients and healthy controls [10], previous work on eye-movement abnormalities in schizophrenia has been performed in laboratory settings. Recent studies in healthy participants have documented differences in eye-movement behavior measured in the laboratory as compared to real-life scenarios [11, 12]. Further, a real-life gaze-tracking study on neurological patients (patients with either idiopathic Parkinson's disease or progressive supranuclear palsy [13]) has demonstrated that mobile eye tracking in natural environments offers a simple, rapid, and reliable tool with good acceptance by the patients.

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Additionally, it showed results partially distinct from laboratory measurements. Accordingly, we aimed at investigating how well eye-movement abnormalities found in schizophrenia patients in laboratory studies transfer to real-world settings. That is, we asked whether some of the differences between schizophrenia patients and healthy controls could be attributed, at least partly, to the laboratory measurement settings. These typically constrain movements (e.g., by restraining the head) and focus on single isolated aspects, whereas real-world tasks usually induce interaction of multiple sensory and eye-movement systems. Differences between laboratory data as reported in the literature and real-world scenarios could point toward compensatory mechanisms in oculomotor control in schizophrenia, which are only available during natural vision. Moreover, the simplicity of modern mobile eye trackers offers the opportunity to be used as a tool in the daily clinical routine. Importantly, even if we find differences, this will not invalidate laboratory eye-movement experiments. To the contrary, we consider laboratory and real-world measurements complementary, in that they shed light on the question how oculomotor deficiencies as measured in the laboratory manifest in patients' activities of daily living.

Active visual tracking of objects during self-motion is a common behavior during everyday life [14]. However, self-motion through an environment induces one of the most fundamental causes for differences between eye movements in the laboratory and the real world. During walking, the eye-movement system encounters distinct demands as compared to sitting still in the laboratory, which is reflected in qualitatively different oculomotor behavior [15, 16]. For example, while tracking movements as performed in the laboratory are typically restricted to eye movements, tracking behavior in the real world is usually accompanied by head movements and vestibular–ocular reflexes. Therefore, real-world oculomotor function faces the additional challenge to integrate self-motion information in order to operate optimally. Yet, in turn, oculomotor deficits may also be compensated by other effectors. The usually required smooth eye movements during visual tracking of a target are impaired in schizophrenia patients when tested in laboratory settings. At the cortical level, the processing of self-motion signals takes place primarily in the dorsal visual pathway [17]. Due to impairments in the magnocellular pathway, this part of the visual cortical system is suggested to be dysfunctional in schizophrenia [18, 19]. Indeed, some motion sensitive areas seem to be impaired in schizophrenia patients [20, 21]. Hence, we hypothesized that the processing of self-motion information, which in humans as well as non-human primates (NHPs) is explicitly encoded in areas like the ventral intraparietal area (VIP [22–25]) and the medial superior temporal area (MST [26–28]), is dysfunctional in schizophrenia patients when performing activities of daily living.

In the current study, we measured eye-movement parameters in schizophrenia patients and healthy controls using a mobile lightweight eye tracker, the EyeSeeCam (ESC) [29]. The ESC allows examining eye movements with no physical restrictions in a natural setting during simple tasks like walking. We aimed to find differences between schizophrenia patients and healthy controls in fundamental eye-movement parameters such as fixation duration and saccade amplitude as well as impairments in smooth tracking eye movements. Such differences may interact with task demands or depend on the additional sensory information available in natural settings as compared to the laboratory. If so, this would suggest that schizophrenia patients can compensate for specific deficits under certain behavioral or environmental conditions. If true, it would underline the need for addressing real-world situations to complement laboratory measurements toward a full understanding of the mechanisms underlying oculomotor dysfunctions in patients with schizophrenia.

Materials and methods

Twenty schizophrenia patients (ICD 10: F20.0) and twenty healthy age- and sex-matched controls participated in the study. All of them gave their written informed consent. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki. In this

Table 1 Overview of demographic and clinical values of patients and healthy controls

	Patients mean (SD)	Healthy controls mean (SD)	*p* (*T* test)
Age (years)	31.3 (9.4)	33.2 (6.8)	0.48
Sex	M: 17/w: 3	m: 18/w: 2	0.64
In-/outpatient	In: 9/out: 11		
Age of onset (years)[a]	25.8 (4.7)		
Duration of illness (years)	6.7 (7.4)		
No. of episodes	3.9 (3.2)		
CPZ equivalent dose (mg/day)	865 (789)		
PANSS score [66]	65.6 (23.0)		

[a] Age of onset could not be determined precisely in 4 patients

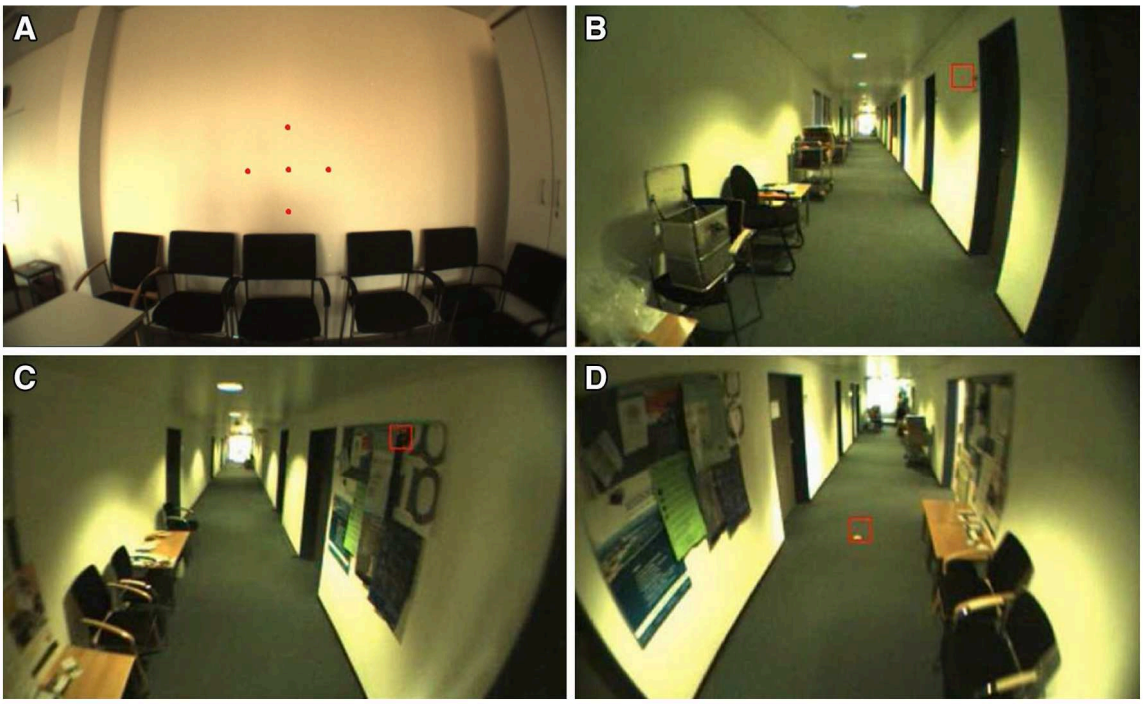

Fig. 1 Illustration of a typical scene during each of four different tasks. Images were taken from the head-mounted camera of the ESC. The *red square* indicates the current gaze position of a participant. **a** Task I: fixating stationary targets with a fixed distance of 7° in a freely selectable and self-paced order as projected by a head-fixed laser pointer of the ESC (enhanced in this figure for visualization). **b** Task II: sitting in a clinic hallway with free gaze. **c** Task III: walking down the hallway with free gaze and **d** Task IV: visually tracking two stationary targets on the floor while walking straight-ahead

study, we focused solely on the paranoid subtype of schizophrenia to minimize variability of test results due to the heterogeneity of this disease. This choice guaranteed to cover the most prevalent subtype. The patients were recruited at the Department of Psychiatry and Psychotherapy at the University of Marburg. For more details on the patient and control groups, see Table 1.

All patients were on neuroleptic medication. Some patients also were administered antidepressants ($n = 6$) and anticholinergics ($n = 3$). Participants were excluded if they had a history of serious head injury, general medical, or neurological disease. All participants had normal or corrected-to-normal vision. In addition, healthy controls were excluded if they or a first-degree relative had a psychiatric disorder. All participants were instructed by an experienced researcher and were able to perform the tasks.

We used a mobile lightweight eye tracker, the EyeSeeCam (ESC), to study binocular eye movements with a sampling rate of 280 Hz, a spatial resolution of 0.02°, and a precision of about 0.1° [30]. Although this does not compare to state-of-the-art laboratory equipment, these values compare well to other mobile eye-tracking systems used in natural environments and allowed us to determine saccadic eye-movement parameters reliably. The system was calibrated before each measurement by matching the gaze direction of each subject with the position of 5 predefined targets, projected with a head-fixed laser pointer to a plain wall in two meter distance. The mean error threshold for a successful calibration was set to 0.5°. Participants were asked to perform different tasks in an indoor environment and were instructed to act as they normally would throughout these tasks.

The paradigm consisted of four different tasks, which are illustrated schematically in Fig. 1. In short, during task I, subjects had to successively fixate predefined targets in a self-chosen order. Afterward, subjects sat in a hallway with free gaze (task II) or walked along that hallway with no additional task (task III). Finally, in task IV, subjects were asked to visually track a fixed spot on the ground while walking toward it. Across the group of patients and controls, the duration of the full set of measurements, i.e., performing all four tasks once including setup and calibration of the eye tracker, ranged from 5 to 10 min.

Video sequences of self-motion and eye position data were analyzed offline using MATLAB 2010b (the MathWorks, Inc., Natick, Massachusetts, USA).

Initially, the raw eye position data recorded with the ESC were analyzed for blinks and other artifacts due to reflections by external light sources. Blinks were identified as the absence of more than 5 samples (18 ms), and eye

traces were cleaned for blink artifacts such that 8 samples (29 ms) before the start of a blink and 12 samples (43 ms) after a blink were not considered for further analysis. For the whole measurement, this resulted in an overall rejection of 2.9 % of all recorded samples from further analysis.

Afterward, horizontal and vertical eye speed was computed by the point-wise derivative of the respective eye-position values. Absolute eye velocities were calculated by taking the square root of the sum of the squared horizontal and vertical eye speed components.

Eye movements were classified as saccades if eye velocity was higher than 100°/s for at least 3 consecutive samples and if the eyes moved more than 0.5° in this period. In addition, a main-sequence analysis (peak velocity/amplitude) of all fast eye movements was performed by computing the power function fit ($v_{\text{peak}} = K * \text{amplitude}^L$) for eye position data from each subject and its corresponding 95 % confidence interval [31]. The remaining 5 % of all potential saccades outside this interval were classified as outliers and were not considered for further analysis. Oculomotor behaviors during which the eye position remained within a 1° - wide window in the horizontal and vertical direction for at least 150 ms were considered fixations.

To evaluate tracking behavior in tasks III and IV, we determined classical eye-in-head gain values (eye velocity divided by target velocity) of the respective eye movements. In a first step, all tracking segments were cleaned for saccadic artifacts such as catch-up saccades to analyze the smooth tracking phase solely. Target velocity was determined in two different ways. Since subjects were free to move their eyes, they typically tracked multiple objects during their way through the hallway. In addition, each subject chose his/her own walking speed. Accordingly, the reference velocity (target velocity) had to be determined individually for each subject and each eye-movement trajectory. To this end and as a first approach, we computed the optical flow field from the head-centered video [32]. Target velocity was considered the velocity of the image part relative to the head which was tracked by the subjects' gaze.

In task IV, subjects had to track one specific object (target) at a time. Thus, target velocity could be easily determined by the temporal derivative of the target position as determined from the head-centered scene. This method was used to compute the gain values. In an additional analysis, we calculated the RMSE (root-mean-square error) of the retinal target velocity. The rationale for choosing the RMSE, just as the gain, is its wide use as a global measure of pursuit performance [33] and its good test–retest reliability [34]. To this end, we analyzed GazeCam videos of the EyeSeeCam, that is, a video sequence obtained from a movable camera which follows the gaze of the subject with a constant latency of about 10 ms [30]. The temporal derivative of the target position within this retinocentric framework served as retinal target velocity. The RMSE corresponds to summing all deviations from this target velocity.

Since most eye-movement parameters during natural vision with free gaze are not normally distributed [35], which also holds true for our data as verified by a Shapiro–Wilk test [36], we used the nonparametric Mann–Whitney *U* test [37] for all statistical analyses. An alpha level of 0.05 was used as threshold for significance. Thus, in task II–IV, we determined the median of each eye movement parameter from each participant separately. Then, the mean and standard deviation of these medians were calculated for the two groups. As an exception, the presence of predefined fixation targets in task I generated a nearly normal distribution of saccadic parameters, which allowed us to calculate the means instead of the medians of each parameter and participant. Additionally, the effect size of each result was computed using the "area under the receiver operating characteristic curve" (AUC) [38]. AUC can be understood as a measure of overlap of two distributions, with separability being minimal at a value of 0.5 and maximal at 0.0 or 1, respectively [39]. The 95 % confidence interval for each effect size was calculated analytically [40].

Finally, as an exploratory post hoc analysis, we correlated (Pearson's correlation) all eye-movement parameters with the patients' PANSS score and the corresponding subscores in every task.

Results

Twenty schizophrenia patients and twenty healthy age- and sex-matched controls participated in the study. All participants had to do four different oculomotor tasks in a natural environment.

Eye-tracking parameters

We found no significant difference in blink frequency between patients and controls, which otherwise could have compromised the analysis of saccade frequency or fixation duration differently (task I: mean 0.198/s ± 0.408/s vs. 0.135/s ± 0.226/s; $Z = 0.520$; $p = 0.603$; AUC = 0.546 [0.366 0.727]; task II: mean 0.457/s ± 0.314/s vs. 0.301/s ± 0.140/s; $Z = 1.447$; $p = 0.148$; AUC = 0.635 [0.462 0.808] task III: mean 0.629/s ± 0.311/s vs. 0.486/s ± 0.296/s; $Z = 1.475$; $p = 0.140$; AUC = 0.638 [0.465 0.810]).

Saccades

We determined general saccade features such as frequency, amplitude, and peak velocity for tasks I–III (see Methods for details). During task I, self-initiated saccades between

Table 2 Basic saccadic parameters by task

	Patients Mean (SD)	Controls Mean (SD)	Effect size (AUC)	*U* test	
				Z value	*p* value
Task I (stationary targets)					
Mean saccade amplitude (°)	**5.53 (1.16)**	**6.57 (1.29)**	**0.305 [0.141 0.469]**	**−2.096**	**0.036**
Mean saccade peak velocity (°/s)	270.0 (50.9)	283.2 (43.3)	0.395 [0.219 0.571]	−1.123	0.262
Main-sequence fit *K* value	**160.0 (37.7)**	**130.7 (58.9)**	**0.690 [0.525 0.855]**	**2.044**	**0.041**
Main-sequence fit *L* value	0.328 (0.13)	0.468 (0.21)	0.338 [0.168 0.507]	−1.745	0.081
Mean saccade frequency (1/s)	**1.57 (0.57)**	**1.06 (0.54)**	**0.728 [0.570 0.885]**	**2.448**	**0.014**
Task II (free gaze)					
Median saccade amplitude (°)	2.641 (1.25)	3.014 (0.78)	0.363 [0.190 0.535]	−1.474	0.140
Median saccade peak velocity (°/s)	218.6 (39.2)	218.0 (19.5)	0.488 [0.306 0.669]	−0.122	0.903
Main-sequence fit *K* value	162.37 (23.50)	152.92 (14.78)	0.618 [0.442 0.793]	1.256	0.209
Main-sequence fit *L* value	0.339 (0.11)	0.352 (0.04)	0.550 [0.370 0.730]	−0.527	0.598
Mean saccade frequency (1/s)	**0.80 (0.62)**	**1.13 (0.25)**	**0.235 [0.086 0.384]**	**−2.854**	**0.004**
Task III (walking)					
Median saccade amplitude (°)	**3.186 (1.41)**	**4.247 (1.22)**	**0.268 [0.111 0.424]**	**−2.512**	**0.012**
Median saccade peak velocity (°/s)	260.1 (56.1)	283.0 (47.5)	0.368 [0.194 0.541]	−1.419	0.156
Main-sequence fit *K* value	190.31 (42.08)	179.02 (29.69)	0.580 [0.402 0.758]	0.852	0.394
Main-sequence fit *L* value	0.307 (0.07)	0.348 (0.06)	0.338 [0.168 0.507]	−1.745	0.081
Mean saccade frequency (1/s)	2.51 (1.59)	2.75 (1.07)	0.423 [0.244 0.601]	−0.826	0.409
Overall					
Median saccade amplitude (°)	2.825 (1.15)	3.175 (0.89)	0.345 [0.178 0.528]	−1.665	0.096
Median saccade peak velocity (°/s)	237.2 (38.5)	239.0 (27.9)	0.473 [0.290 0.658]	−0.285	0.776
Main-sequence fit *K* value	**181.04 (26.64)**	**167.21 (26.63)**	**0.690 [0.525 0.855]**	**2.044**	**0.041**
Main-sequence fit *L* value	**0.312 (0.053)**	**0.349 (0.062)**	**0.318 [0.151 0.484]**	**−1.961**	**0.0499**
Mean saccade frequency (1/s)	1.23 (0.74)	1.32 (0.25)	0.400 [0.223 0.577]	−1.069	0.285
Median saccade peak velocity (°/s) for saccade amplitudes of					
1°–2°	**187.1 (*n* = 1097)**	**181.4 (*n* = 1138)**	**0.535 [0.512 0.559]**	**2.901**	**0.004**
2°–3°	**210.1 (*n* = 587)**	**203.3 (*n* = 633)**	**0.548 [0.516 0.581]**	**2.926**	**0.003**
3°–4°	228.4 (*n* = 399)	220.7 (*n* = 449)	0.518 [0.479 0.557]	0.904	0.366

Median saccade amplitudes, peak velocities, frequency, and main-sequence fit parameters for fixating stationary targets in a freely selectable and self-paced order (task I) both free exploration tasks (task II and task III) and the whole measurement (Overall). In task IV, saccades were not analyzed further. Significant parameters are highlighted in bold

predefined targets showed a significantly larger undershoot in the patient population as compared to healthy controls (Table 2, task I). In contrast, differences in saccade peak velocity between groups did not reach significance. Accordingly, the difference in the main-sequence as represented by the two fitting parameters of the power function only tended to be statistically different (Table 2, task I). Additionally, patients showed a significantly higher saccade frequency as represented by a higher rate of alternating gaze between the predefined targets. Finally, inpatients showed significantly less saccades per second (mean 1.287/s ± 0.456/s) than outpatients (mean 1.806/s ± 0.556/s; $Z = -2.086$; $p = 0.037$; AUC = 0.212 [0.010 0.414]).

In task II, subjects were free to move their eyes. Here, neither saccade amplitude nor peak velocity showed a significant difference between groups which was also reflected by the fitting parameters of the main-sequence (Table 2, task II). Contrary to task I, saccade frequency was significantly lower in patients as compared to healthy controls.

In task III, we found no difference in saccade frequency, but a significantly smaller median saccade amplitude in patients, which was mainly due to less saccades to the periphery as compared to healthy controls. On the other hand, saccade peak velocity and parameters of the main-sequence were not significantly different in this task (Table 2, task III).

When analyzing the saccades of the entire measurement without differentiating between certain tasks, which resembles the diversity of saccadic eye movements during everyday life, differences in the main-sequence fit parameters between patients and controls became significant (Table 2, Overall; Fig. 2). Although not statistically different, the

Table 3 Correlations of saccade parameters with patients' symptom ratings by task

Eye-movement parameter	PANSS item	Pearson's correlation coefficient ($df = 18$)	p value
Task I (stationary targets)			
Mean saccade amplitude (°)	Poor rapport	−0.594	0.006
Mean saccade amplitude (°)	Lack of spontaneity and flow of conversation	−0.538	0.014
Mean saccade amplitude (°)	Stereotyped thinking	−0.481	0.032
Mean saccade amplitude (°)	Lack of judgment and insight	−0.540	0.014
Mean saccade amplitude (°)	PANSS negative	−0.561	0.010
Mean saccade amplitude (°)	PANSS general	−0.482	0.031
Mean saccade amplitude (°)	PANSS total	−0.570	0.009
Mean saccade peak velocity (°/s)	Lack of spontaneity and flow of conversation	−0.452	0.045
Mean saccade peak velocity (°/s)	PANSS negative	−0.511	0.021
Task II (free gaze)			
Mean # saccade (1/s)	Depression	0.480	0.032
Mean # saccade (1/s)	Motor retardation	0.492	0.028
Median saccade amplitude (°)	Motor retardation	0.608	0.004
Median saccade peak velocity (°/s)	Somatic concern	0.491	0.028

Significant correlations of saccade eye-movement parameters with PANSS scores and subscores for task I and task II. Task III and task IV did not show any significant correlations

quality of the main-sequence fits as represented by the R^2 values tended to be worse in schizophrenia patients (Overall: mean $R^2 = 0.545 \pm 0.185$) than in healthy controls (Overall: mean $R^2 = 0.655 \pm 0.184$; $Z = -1.91$; $p = 0.057$; AUC = 0.323 [0.155 0.490]). The difference of saccade parameters between schizophrenia patients and healthy controls became particularly prominent when analyzing peak velocities of saccades within specific amplitude ranges. Patients showed the most significant differences in saccade peak velocities as compared to controls for small amplitudes, e.g., 1°–2° or 2°–3°. This difference in saccade peak velocities disappeared for saccade amplitudes between 3°–4° and higher amplitude ranges. Across the whole measurement range, neither saccade amplitude nor peak velocity or frequency showed a significant difference between groups.

Some of the eye-movement parameters described here correlated with the patients' PANSS items (Table 3), notably a negative correlation between mean saccade amplitude in task I and a lack of judgment and insight ($r(18) = -0.540$; $p = 0.014$; Pearson's correlation) and a positive correlation of median saccade amplitude in task II and motor retardation ($r(18) = 0.608$; $p = 0.004$; Pearson's correlation). There was no correlation of the saccade parameters with any PANSS item during task III and task IV or with CPZ equivalent dose (all $p \geq 0.4$).

Fixation

During free gaze in task II (Fig. 3: free gaze), median fixation duration was significantly longer in patients (0.521 s ± 0.182 s vs. 0.394 s ± 0.045; $Z = 2.151$; $p = 0.032$; U test; AUC = 0.700 [0.537 0.863]) and they fixated less often (1.24/s ± 0.51/s) than healthy controls (1.67/s ± 0.23/s; $Z = -2.962$; $p = 0.003$; U test; AUC = 0.225 [0.079 0.371]). There was a significant correlation between the PANSS item grandiosity in patients with schizophrenia and median fixation duration during this task ($r(18) = 0.516$; $p = 0.020$; Pearson's correlation).

Task I, in which subjects had to fixate predefined targets in a freely chosen random order (Fig. 3: stationary targets), showed the exact opposite result. Median fixation duration was significantly shorter in patients (0.481 s ± 0.227 s) as compared to healthy controls (1.053 s ± 0.766 s; $Z = -3.246$; $p = 0.001$; U test; AUC = 0.199 [0.060 0.338]), whereas fixation frequency was significantly higher for patients than for controls (1.72/s ± 0.52/s vs. 1.22/s ± 0.56/s; $Z = 2.61$; $p = 0.009$; U test; AUC = 0.743 [0.588 0.897]). Furthermore, there was a correlation in schizophrenic patients between anxiety and mean number of fixations per second ($r(18) = 0.561$; $p = 0.010$; Pearson's correlation) during this task.

Remarkably, the above finding of an inversion of fixation behavior of patients and controls between free and guided gaze was accompanied by (or due to) the fact that the median fixation duration in patients did not differ significantly between the two tasks (task I: 0.481 s ± 0.227 s vs. task II: 0.521 s ± 0.182; $Z = -1.069$; $p = 0.285$; U test; AUC = 0.400 [0.223 0.577]), while healthy controls showed a significant modulation of this value (task I:

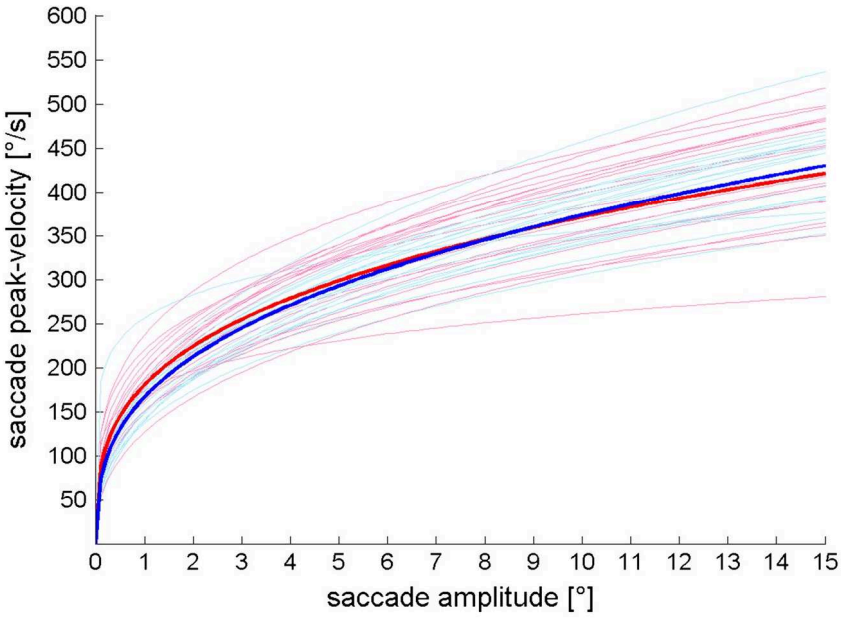

Fig. 2 Main-Sequence fit-functions for all participants. Individual data for schizophrenia patients were plotted in *light red*, healthy controls in *light blue*. The mean fit-function of each group is highlighted with a *bold red line* for schizophrenia patients and a *bold blue line* for healthy controls. An initial steeper rise of the mean fit-function in schizophrenia patients is clearly visible for small amplitudes. For higher saccade amplitudes, the slope of the main-sequence mean fit-function became less steep in schizophrenia patients as compared to healthy controls

1.053 s ± 0.766 s vs. task II: 0.394 s ± 0.045; $Z = 3.855$; $p = 0.0001$; U test; AUC = 0.858 [0.738 0.977]). There were no qualitative or statistical differences in the fixation results, when eye traces were either cleaned for blink artifacts or not.

There was no correlation of any of the fixation parameters with CPZ equivalent dose (all $p \geq 0.096$).

Tracking eye movements

In task III, the subjects looked at self-chosen targets (e.g., posters at the wall or chairs) while walking through the hallway. This oculomotor behavior induces visual tracking. We analyzed such tracking periods by evaluating the gain of the eye movement. Surprisingly, we found no significant difference in gain between patients (1.316 ± 0.386) and healthy controls (1.246 ± 0.248; $Z = 0.500$; $p = 0.617$; U test; AUC = 0.548 [0.367 0.728]) during such spontaneous tracking.

The active tracking of stationary targets on the ground during task IV was also quantified by computing the oculomotor gain values which, again, did not show a significant difference between groups (mean 0.862 ± 0.302 vs. 0.902 ± 0.213; $Z = -0.448$; $p = 0.654$; U test; AUC = 0.470 [0.341 0.599]). Yet, the mean RMSE of the foveal velocity, as measure of tracking precision, was significantly higher in patients (23.52°/s ± 10.42°/s) than in healthy controls (16.98°/s ± 6.00°/s; $Z = 2.385$; $p = 0.017$; U test; AUC = 0.671 [0.541 0.801]) during this task.

There was no correlation of the parameters during tracking eye movements with any PANSS item or with CPZ equivalent dose (all $p \geq 0.136$).

Discussion

In this study, we investigated oculomotor behavior in schizophrenia patients and healthy controls during natural behavior, where participants could freely move their eyes, head, and body. For specific oculomotor parameters, such as fixation duration and frequency, we found significant differences between the groups. Some of these differences resembled those reported under laboratory conditions, such as decreased exploratory eye movements [8, 9], while others (e.g., tracking eye movement gain) seem to reach normal performance during natural vision. This might be a characteristic feature of eye-movement behavior in real-life environments which possibly trigger as of yet unknown compensatory mechanisms.

Saccades

In task I, subjects had to successively fixate predefined targets in a self-chosen serial order. Similar to results obtained from experiments in a laboratory environment [6, 7], we found a systematic saccadic undershoot in schizophrenia patients. Other studies performed in laboratory environments did not find shortened saccade amplitudes [41] or reported even an overshoot [42]. A possible explanation for these seemingly contradictory results could be the discrete ranges of saccadic amplitudes employed in the different studies. While Schmid-Burgk and colleagues [6, 7] analyzed a variety of saccadic amplitudes, Levin et al. [41] did not analyze each amplitude range separately for its accuracy. This latter approach might have concealed an undershoot for certain saccade amplitudes. When considering the full range of amplitudes, we found no significant difference of peak velocity between patients and

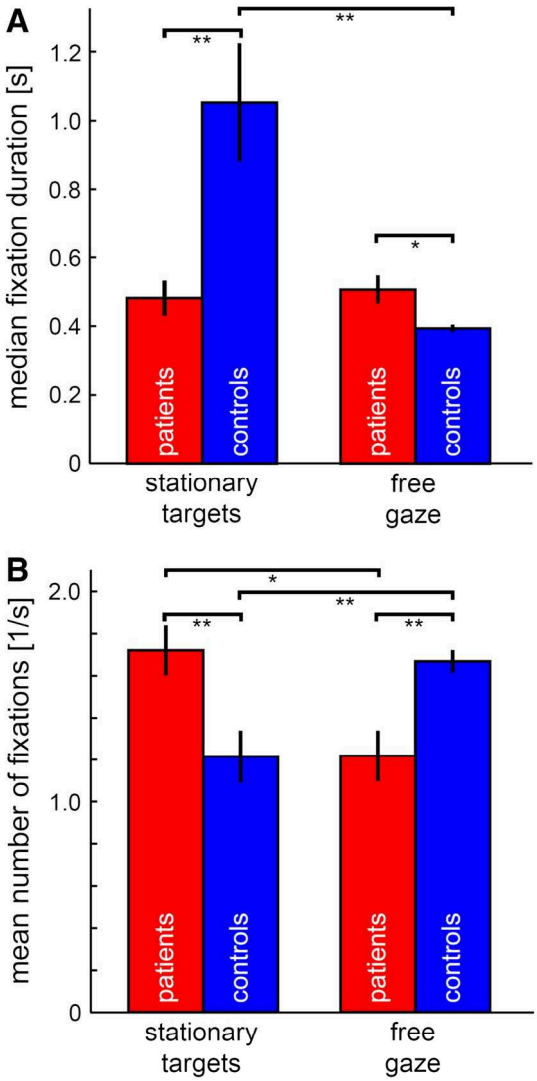

Fig. 3 Median fixation duration (**a**) and mean fixation frequency (**b**) during task I (stationary targets) and task II (free gaze). When subjects had to fixate predefined targets in a freely chosen random order, patients fixated significantly shorter and more often than healthy controls. During free gaze it was the other way around. Remarkably, the median fixation duration in patients did not differ significantly between the two tasks, while healthy controls showed a significant modulation of this value. *Vertical black bars* indicate standard error. *Horizontal bars* and the corresponding *stars* indicate significant differences between the two connected values $*p < 0.05$; $**p < 0.01$

controls. When splitting analysis by saccade amplitudes, however, our results during free gaze showed the most prominent differences in saccade peak velocity between patients and controls for small amplitudes (i.e., 1°–3°). This latter amplitude range is most common during natural vision [35] but rarely examined in laboratory settings. Hence, our present results, at least to some extent, reconcile the apparently conflicting findings in the literature.

The main-sequence of saccades only showed significant differences between patients and controls when comparing all saccades during all tasks. The slightly worse R^2 values in schizophrenia patients could mainly be attributed to the higher variability of saccade parameters within the patient cohort (see standard deviations of saccade amplitudes and peak velocities in Table 2) due to the heterogeneity of the disease. The fit parameters of the power functions indicated an initially steeper slope of functions obtained from patients, which levels out and eventually drops below the level of healthy controls. This functional characteristic might be further evidence that the examined saccade amplitude ranges play a crucial role when studying saccades of schizophrenic patients.

Our results indicate a general impairment of visually guided saccades in schizophrenia patients, which has also been deduced from fMRI findings showing a decreased activation in supplementary and frontal eye fields during saccades [43, 44]. Other studies suggested an impaired prediction of the sensory consequences of one's own actions [45] and deficient self-monitoring in schizophrenia patients [46], which might result in an incorrect saccade planning. This is supported by studies indicating a generally impaired efference copy mechanism in patients with schizophrenia [47–49]. The negative correlation of the saccade amplitude with the severity of symptoms in our study is in line with these findings and offers an explanation for the observed saccadic undershoot during task I in schizophrenia. In our current study, however, differences in saccade parameters between patients and controls largely depended on the amplitude range under consideration. This amplitude-dependent impairment and its normalization in certain ranges demonstrate the ability of patients to compensate, at least partially, for oculomotor inaccuracies during free natural vision.

Fixation

Oculomotor parameters such as fixation duration and fixation frequency were differently influenced by the behavioral task or the presence or absence of predefined targets. During free gaze and without any additional behavioral task, patients fixated significantly longer and less often than healthy controls. This is in line with a recent study by Egaña et al. [9], investigating free viewing of natural images in the laboratory. In our study, median fixation duration was correlated with the PANSS item grandiosity in schizophrenia patients, indicating that some patients might have drifted off in their imagination during this task. During the fixation of given targets and the instruction to look at them in a self-chosen and self-paced order, however, patients leaped from target to target more than twice as fast as compared to healthy controls. This performance was significantly correlated with anxiety in schizophrenia patients leading to even shorter fixation durations and

more fixations per second the more anxious a patient was. However, the observed differences between the tasks were mainly due to a task-specific change in the median fixation duration of healthy controls, while schizophrenia patients fixated almost equally long in both tasks. These results could be based on different bottom-up and top-down processing of visual and non-visual information in schizophrenia patients and healthy controls. It has been argued, for example, that the deployment of attention, for which gaze allocation is a proxy [50, 51], is altered in patients with schizophrenia. Various studies have shown a higher distractibility [52] or the inability to focus attention on salient cues [53] in schizophrenia patients. Yet, the lack of difference in fixation duration during task I and task II in schizophrenia patients of our study implies a more subtle influence of attention and task demands on patients as compared to controls. This suggests that alteration of task performance is differently modulated in patients with schizophrenia and that top-down influences might be less influential for their behavior as compared to healthy controls.

Overall eye-movement patterns of schizophrenia patients showed less exploratory behavior such as saccades to the periphery. This result might be indicative for a generally lower interest of patients in exploring their environment. Earlier studies showed similarly decreased exploratory eye movements in schizophrenia patients in laboratory settings [8, 9] or during unfamiliar tasks in a real-life scenario [10]. We show that this finding is also valid during natural vision in everyday life and therefore might influence perception as a whole in schizophrenia patients.

Tracking eye movements

The analysis of the visual tracking of a stationary target on the ground during self-motion revealed an unexpected result. Although related to smooth-pursuit eye movements (i.e., keeping a visually moving object stationary on the retina), we could not find the typical reduced tracking gain, which has been reported for schizophrenia patients and even their first-degree relatives under laboratory conditions [1–4, 6]. Instead, patients and controls revealed high gain tracking of stationary targets and freely chosen objects. Active tracking of optic flow elements with a gain of almost 1.0 has previously been described under laboratory conditions for healthy subjects [14]. Our current findings indicate that patients might be able to partly compensate for their poor tracking performance during smooth pursuit in the laboratory, e.g., using additional sensory cues (optic flow, vestibular signals) when tracking a target in a real-world environment. This view is supported by Holzman [54], who identified the main source of poor tracking performance in schizophrenia patients as a deficit in velocity sensitivity. In his study, the velocity discrimination of patients got worse when additional non-velocity stimulus cues were eliminated and subjects were forced to rely solely on velocity cues. In natural behavior, several sensory and motor signals interact (e.g., a combination of pursuit and vergence eye movements), which might aid the visual and oculomotor system during target tracking. Additionally, in our paradigm, head movements may have compensated for the otherwise impaired tracking gain. This idea is supported by a recent study which showed abnormal eye–head coordination in schizophrenia patients expressed by an uneconomic over-performance of head movements [55]. Finally, a generally higher demand during natural tasks might have influenced the tracking performance of schizophrenic patients. Shagass and colleagues [56] showed that smooth-pursuit gain in the laboratory improved significantly when the patients had to read numbers shown on the tracking target. The authors argued that the improved gain was due to an increased attentional load, which might also apply to tracking eye movements in natural environments.

Contrary to the gain-tracking performance, the RMSEs of the foveal velocity differed significantly between schizophrenia patients and healthy controls. This result suggests a generally more imprecise tracking with numerous small deviations from an optimal tracking behavior in patients with schizophrenia.

Since re-inviting the same cohort of patients to laboratory measurements was not feasible, we compared the real-world data to common findings from laboratory data reported in the literature. It is self-evident that there is no one-to-one mapping between such tasks.

For example, smooth-pursuit eye movements with fixed head in the laboratory and tracking (eye)movements in the real world serve the same purpose: keep a visually moving object stationary on the retina. However, in the former case only, the eyes are moving, whereas in the latter, eye, head, and possibly body contribute. Hence, the real-world situation requires a higher level of integration, but also offers mechanisms for compensation. To further investigate the differences in tracking performance and the possible contribution of head movements and additional sensory signals, a future study could analyze the tracking of a thrown object while participants are not moving. This type of experiment might be more comparable to smooth pursuit in the laboratory and might reduce the gap between the reported reduced gain in the literature and the real-world data in our study.

Another challenge for comparing data between studies—and even for between-subject designs in the same study—is the heterogeneity of schizophrenia, which is further amplified by potential effects of medication. These limitations notwithstanding, any differences between our results and studies performed in the laboratory may suggest the influence of as of yet unknown distinct or additional

mechanisms to eye movements of schizophrenia patients in natural environments, which would point toward new research objectives of future studies and will help to complement the overall picture of this disease.

Schizophrenia patients perform worse in a variety of visual motion tasks, such as discrimination of velocity [57] and motion direction [20], localization and visual backward masking tasks [58]. This may be caused by a dysfunction in areas of the visual motion system, i.e., among others in human middle temporal area (MT) and MST [20, 59], respectively. A dysfunction in those areas in schizophrenia patients could also contribute to the more noisy tracking behavior in our study. Studies in non-human primates implicate that another area of the parietal cortex, the ventral intraparietal area (VIP), is critically involved in the encoding of self-motion [23, 60, 61] and smooth-pursuit eye movements by guiding and coordinating smooth eye and head movements within near-extrapersonal space [62–64]. A functional equivalent of macaque VIP has been identified in human [22]. Accordingly, human area VIP might also play a crucial role in the observed eye-movement dysfunction in schizophrenia patients. This view is supported by Chen et al. [20] who showed a global, but not local, motion processing deficit in patients with schizophrenia. The contribution of multisensory areas like area VIP [65] to the eye-movement behavior in schizophrenia patients might have been hidden in most previously conducted laboratory studies and becomes especially interesting in natural contexts by providing and combining additional sensory information. Hence, further investigations of a functional impairment of the areas within the parietal cortex of schizophrenia patients are needed to better understand the observed eye-movement deviations from healthy controls during natural behavior.

In conclusion, the study of eye movements in natural environments showed differences in basic eye-movement parameters between schizophrenia patients and healthy controls during simple everyday tasks, which were strongly modulated by the task demands. Furthermore, our data suggest that patients can overcome some oculomotor impairments, which become obvious in laboratory studies (e.g., reduced gain during tracking eye movements), by as yet unknown compensatory mechanisms or strategies. These might include an improvement in performance due to higher task engagement and additional sensory input (optic flow, vestibular signals) during natural tasks as well as the possibility to perform unrestricted head movements. Being aware of the multitude of differences between our real-world tasks and typical laboratory measurements, our results provide a first step toward analyzing real-world oculomotor behavior in schizophrenia. Teasing apart the sources of differences and commonalities between laboratory results and real-world data will be an important issue for future research. In any case, our results underline the need to complement laboratory experiments with real-word data (and vice versa) in order to achieve a complete picture of oculomotor dysfunctions in schizophrenia and their implications for patients' activities of daily living.

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Conflict of interest The authors declare no competing financial interests.

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Effects of aging on eye movements in the real world

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The effects of aging on eye movements are well studied in the laboratory. Increased saccade latencies or decreased smooth-pursuit gain are well established findings. The question remains whether these findings are influenced by the rather untypical environment of a laboratory; that is, whether or not they transfer to the real world. We measured 34 healthy participants between the age of 25 and 85 during two everyday tasks in the real world: (I) walking down a hallway with free gaze, (II) visual tracking of an earth-fixed object while walking straight-ahead. Eye movements were recorded with a mobile light-weight eye tracker, the EyeSeeCam (ESC). We find that age significantly influences saccade parameters. With increasing age, saccade frequency, amplitude, peak velocity, and mean velocity are reduced and the velocity/amplitude distribution as well as the velocity profile become less skewed. In contrast to laboratory results on smooth pursuit, we did not find a significant effect of age on tracking eye-movements in the real world. Taken together, age-related eye-movement changes as measured in the laboratory only partly resemble those in the real world. It is well-conceivable that in the real world additional sensory cues, such as head-movement or vestibular signals, may partially compensate for age-related effects, which, according to this view, would be specific to early motion processing. In any case, our results highlight the importance of validity for natural situations when studying the impact of aging on real-life performance.

Keywords: eye movements, aging, real-world gaze, natural environment, self-motion, saccades, tracking eye-movements

INTRODUCTION

As we are getting older, the function of the visual system appears to deteriorate. Not only does visual acuity decline in the elderly, but perception (e.g., Billino et al., 2008; Lich and Bremmer, 2014) and eye-movement parameters are also altered (Morgan, 1993). Increased saccadic latencies (Abel et al., 1983; Moschner and Baloh, 1994; Munoz et al., 1998; Klein et al., 2000) and decreased smooth-pursuit gain (Moschner and Baloh, 1994; Ross et al., 1999) are common findings in the literature, while the results for other oculomotor parameters like saccade peak-velocity are inconclusive. Some studies found a decrease during senescence (Warabi et al., 1984; Sharpe and Zackon, 1987; Irving et al., 2006), whereas others could not show a significant correlation of age and saccade peak velocity (Henriksson et al., 1980; Munoz et al., 1998).

In the last decades, the study of eye movements has increased in relevance as gaze serves as an easily accessible, reliable, safe and fast proxy for cognitive processes and as tool to identify possible functional impairments of the brain (Leigh and Zee, 2006). As an example, the measurement of saccade amplitude and velocity offers an indication of the functionality of the saccade generating circuitry in the brainstem (Sparks, 2002). Certain eye-movement characteristics may extend the knowledge of the mechanism underlying some neurological and psychiatric diseases (Gooding and Basso, 2008; Pinkhardt et al., 2008; Marx et al., 2012; Dowiasch et al., 2014), and might in the long-run, support diagnosis in the clinical routine.

Self-motion through an environment induces one of the most fundamental causes for differences between eye movements in the laboratory and the real world. For example, during walking, the eye-movement system encounters distinct demands as compared to sitting still in the laboratory, which is reflected in qualitatively different oculomotor behavior ('t Hart et al., 2009; 't Hart and Einhäuser, 2012). For example, keeping the eyes on a target that is stationary in the world turns from a mere fixation in the laboratory into a tracking eye-movement during self-motion (Niemann et al., 1999), since the projection of every location in our visual field moves across the retina. Likewise, smooth-pursuit eye-movements as performed in the laboratory are often accompanied by head movements and vestibular-ocular reflexes during free real-world movement. Therefore, these eye movements have to integrate self-motion information in order to operate optimally. At the cortical level, this leads to a massive involvement of areas of the dorsal pathway where the processing of self-motion signals primarily takes place (Bremmer et al., 2000). Especially areas like the ventral intraparietal area (VIP; Bremmer et al., 2001, 2002a; Britten, 2008; Wall and Smith, 2008; Chen et al., 2011) and the medial superior temporal area (MST; Duffy and Wurtz, 1991; Bremmer et al., 1999; Gu et al., 2008; Pitzalis et al., 2013) get activated not only by visual but also by vestibular self-motion signals.

Despite the increasing interest in real-word eye-tracking and despite the abundance of literature on how eye movements in the laboratory are affected in healthy aging, to the best of our knowledge, no study has addressed the effects of healthy aging on real-world eye-movement behavior. Such a transfer to the real world, however, seems particularly important, as an increasing number of studies on eye movements in real-world environments and during everyday tasks (e.g., Land et al., 1999; Hayhoe and Ballard, 2005) raise substantial doubt as to whether results from the laboratory can be directly transferred to real-world scenarios ('t Hart et al., 2009; Foulsham et al., 2011; Tatler et al., 2011; 't Hart and Einhäuser, 2012). Since these studies have typically been performed with small samples and within a homogenous age group, they left possibly existing effects of age on real-world eye-movement behavior so far unaddressed. Patient studies on oculomotor deficiencies in disease, in turn, typically include a set of age-matched healthy controls and often span a wider age range, but do not typically assess the factor age explicitly. In this study, we draw on such control data from earlier patient studies to close the gap and test if and if so to what extent age relate to eye movements in a comparably unconstrained real-world setting. Specifically, we tracked participants' eye movements while they walked in a corridor either looking around freely or tracking a stationary target on the floor during walking. Since re-inviting the same cohort of participants to laboratory measurements was not feasible, we compared the real-world data in our study to common findings from laboratory studies reported in the literature. It is self-evident that there is no 1-to-1 mapping between such tasks. These limitations notwithstanding, any differences between our results and studies performed in the laboratory may suggest how age-related changes in the healthy brain affect gaze behavior in real-life situations. Such findings would underline the need for addressing real-world tasks to complement laboratory measurements towards a full understanding of the mechanisms underlying oculomotor changes during healthy aging and might point towards new research objectives of future studies.

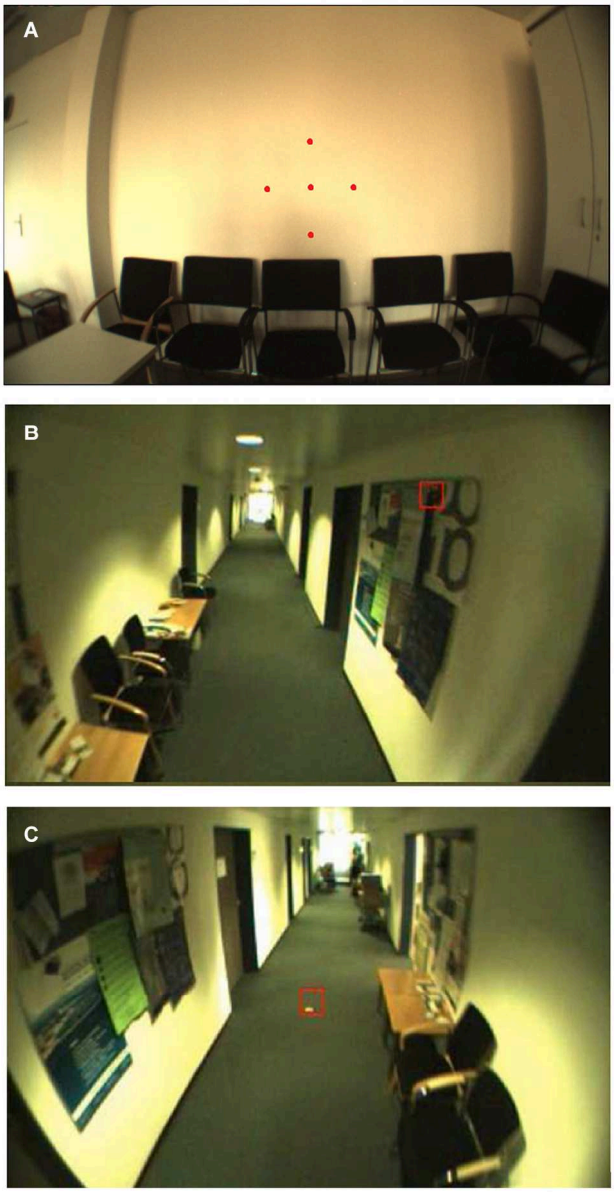

FIGURE 1 | Illustration of a typical scene during calibration and the two tasks. Images were taken from the head mounted camera of the ESC. The red square indicates the current gaze position of a participant. **(A)** Calibration: Fixating stationary targets with a fixed distance of 7° as projected by a head-fixed laserpointer of the ESC (enhanced in this figure for visualization). **(B)** Task I: Walking down the hallway with free gaze and **(C)** Task II: visually tracking two stationary targets on the floor while walking straight-ahead.

METHODS

SUBJECTS

The eye movements of 34 participants (31 male, 3 female) between the age of 25 and 85 (mean = 46y ± 18.5y) were analyzed during two everyday tasks in the real world. All participants were originally recruited as healthy controls for patient studies on eye movements in natural environments (Marx et al., 2012; Dowiasch et al., 2014). Each participant had normal or corrected to normal vision and no history of neurological or psychiatric disease. Two of the tasks in these two studies were identical and are used for the present analysis. Both studies were approved by the local ethics committee and were in accordance with the Declaration of Helsinki. All participants gave their written informed consent.

DATA ACQUISITION

Binocular eye-in-head movements were recorded with a mobile light-weight eye tracker, the EyeSeeCam (ESC), at a sampling rate of 280 Hz, a spatial resolution of 0.02° and a precision of about 0.1° (Schneider et al., 2009). This allowed us to record and analyze saccadic eye-movements during walking with free gaze reliably. The ESC records a head-centered video with a head-fixed camera and provides a video sequence obtained from a movable camera (GazeCam) which follows the gaze of the participant with a constant latency of about 10 ms (Schneider et al., 2009). Before each measurement the system

was calibrated by matching the gaze direction of the subject with the position of 5 predefined targets, which were projected to a plain wall at a distance of 2 m by a head fixed laser pointer (**Figure 1A**). The mean error threshold for calibration was set to 0.5°. After successful calibration, the participants were asked to perform two different tasks in an indoor environment and to act as they normally would throughout these tasks.

BEHAVIORAL TASKS

In the first task participants had to walk along a hallway for about 35 m with free gaze and no additional instruction (**Figure 1B**). For the second task, they were asked to visually track a stationary orange colored spot with a diameter of 10 cm on the ground (dark green carpet) while walking towards it, starting about 10 m away from the spot (**Figure 1C**). Each participant was free to choose his/her own walking speed. The duration of the full set of measurements including setup (∼1 min), accustoming (at least 2 min; participants indicated when they feel ready to perform the tasks) and calibration (∼1 min) of the eye tracker ranged from 5 to 10 min per participant.

Recorded eye-position data and video sequences were analyzed offline using MATLAB 2010b (The MathWorks, Inc., Natick, Massachusetts, USA). In a first step, raw eye-position data was inspected for blinks or other recording artifacts due e.g., to reflections by external light sources. Blinks were classified by the absence of more than 5 samples (18 ms) and eye traces were cleaned for blink artifacts by deleting 8 samples (29 ms) before the start of a blink and 12 samples (43 ms) after a blink. Saccades were detected if eye velocity was higher than 100°/s for at least 3 consecutive samples and if the eyes moved more than 0.5° in this time period. This conservative threshold guaranteed a low false-positive rate for saccade detection, since eye movements during real-life measurements contain extensive dynamics (e.g., due to vestibulo-ocular reflexes or vergence eye movements) and are generally noisier than under controlled laboratory settings. Furthermore, a main-sequence analysis (peak velocity/amplitude) of thus defined saccades was performed by computing the power function fit ($v_{peak} = K * amplitude^{L}$) and its corresponding 95% confidence interval for each subject (Bahill et al., 1975). All saccades outside this interval were classified as outliers and were not considered for further analysis. Additionally, the saccade velocity profile was characterized by using the q-value, which is defined as the ratio of peak- and mean velocity (v_{peak}/v_{mean}; Inchingolo et al., 1987). Finally, saccade amplitude, mean- and peak-velocities were separately analyzed for each of the four cardinal directions (right, left, up, and down). Therefore only saccades with a mean velocity component of more than 100°/s in one of the four directions were considered for analysis to exclude saccades with no specific cardinal direction.

The tracking performance of each participant was quantified by eye-in-head gain values (eye velocity divided by target velocity) and the RMSE (root mean square error) of the retinal target velocity. The rationale for choosing the RMSE, just as for the gain, was its wide use as a global measure of pursuit performance (Smyrnis, 2008) and its good test-retest reliability (Gooding et al., 1994). As a first step in analyzing tracking, all tracking segments were cleaned from saccadic artifacts such as catch-up saccades to analyze the smooth tracking phase only. Since subjects were free to move their eyes in Task I, they typically tracked multiple objects during their way through the hallway ("spontaneous tracking"). In this task only tracking segments longer than 200 ms were considered for further analysis. Accordingly, the reference velocity (target velocity) had to be determined individually for each subject and each eye-movement trajectory. To do so, we computed the optical flow field (Gautama and Van Hulle, 2002) from the head centered video recorded by the ESC. Target velocity was considered the velocity of the image part relative to the head which was tracked by the subjects' gaze. Due to technical issues in the recording of the head-centered video, (e.g., caused by blurred video or by considerable frame drops), the optic flow field of the recordings from 4 participants (age: 33, 50, 64, and 69) could not be computed reliably. These 4 subjects were excluded from optic-flow analysis and no free-viewing gain was computed.

In Task II the presence of specific tracking targets allowed us to determine target velocity as the temporal derivative of the target position in the head-centered scene. In addition, the GazeCam videos of the ESC could be used to calculate retinal target velocity as the temporal derivative of the target position within this retinocentric framework. The sum of all deviations from the optimal retinal target velocity (0°/s) corresponds to the RMSE. In this task, six participants (ages: 30, 33, 33, 50, 64, 74) did not show a sufficient tracking of the specified target (e.g., they ignored the target at all) and their data were therefore excluded from the evaluation of tracking performance (i.e., tracking-gain as well as RMSE). In addition the RMSE could not be evaluated precisely due to considerable frame drops in the GazeCam-videos of three other participants (ages: 30,32,53).

STATISTICS

The analyzed eye-movement parameters (saccade amplitude, saccade peak velocity, saccade mean velocity, and the q-value of the saccade velocity distribution in task I as well as tracking gain and RSME in task II) cannot be expected to follow a normal distribution (Land et al., 1999). Hence we used the non-parametric Mann-Whitney-U-Test (Mann and Whitney, 1947) for all statistical analyses. An alpha-level of 0.05 was used as threshold for significance. We characterized each subject's respective eye-movement parameter by the median (over saccades and tracking epochs, respectively) rather than by the mean. To calculate significance we performed a median-split analysis, comparing the older half of participants to the younger half. This resulted in a younger group (n = 17) with a mean age of 30.1 ± 3.0y and an older group (n = 17) with a mean age of 61.8 ± 12.8y. There was no statistical difference in mean age of the younger or older group when comparing the tasks in which participants were excluded and the full group of participants (freeviewing-gain: younger group (n = 15): mean age 29.5 ± 2.6y; older group (n = 15): mean age 60.2 ± 14.7y; tracking-gain: younger group (n = 14): mean age

Table 1 | Basic eye-movement parameters by task.

	Eye-movement parameter		U-test				
			Young (SD)	Old (SD)	*Z*-value	*p*-value	Effect-Size (AUC)
Task I (walking with free gaze)	median saccade amplitude [°]		4.14 (1.31)	3.25 (1.07)	1.894	0.058	0.692 [0.513 0.871]
	median saccade peak-velocity [°/s]		285.6 (51.4)	220.2 (24.2)	3.789	0.0002	0.882 [0.764 1.000]
	median saccade mean-velocity [°/s]		199.2 (29.1)	168.3 (17.8)	3.134	0.0017	0.817 [0.671 0.962]
	median q-value		1.40 (0.06)	1.31 (0.06)	3.479	0.0005	0.851 [0.719 0.984]
	main-sequence fit K-value		185.0 (24.7)	154.4 (22.8)	3.169	0.0015	0.820 [0.676 0.965]
	main-sequence fit L-value		0.335 (0.04)	0.359 (0.08)	−0.689	0.491	0.429 [0.235 0.624]
	mean saccade frequency [1/s]		3.03 (1.37)	1.83 (1.04)	2.582	0.010	0.761 [0.598 0.924]
	mean freeviewing-gain		1.31 (0.31)	1.56 (0.29)	−2.224	0.026	0.259 [0.077 0.441]
	mean blink rate [1/s]		0.474 (0.32)	0.801 (0.57)	−1.826	0.068	0.315 [0.135 0.495]
	median saccade peak-velocity [°/s]	1°–2° (22.5%)	202.9 (35.1)	187.4 (37.1)	2.032	0.042	0.706 [0.530 0.882]
	for certain saccade amplitudes	2°–3° (11.5%)	244.3 (52.9)	207.9 (28.1)	2.342	0.019	0.737 [0.568 0.906]
		3°–5° (14.7%)	251.6 (28.8)	226.9 (18.6)	2.962	0.003	0.799 [0.648 0.951]
		5°–8° (14.6%)	317.0 (34.8)	283.0 (24.9)	2.997	0.003	0.803 [0.652 0.953]
		8°–15° (15.3%)	413.6 (37.0)	363.9 (41.5)	2.514	0.012	0.855 [0.722 0.988]
Task II (tracking targets)	mean tracking-gain		0.957 (0.13)	0.865 (0.22)	1.264	0.206	0.643 [0.436 0.850]
	tracking RMSE		16.99 (6.97)	17.80 (4.90)	−0.680	0.497	0.417 [0.190 0.643]

Computed eye-movement parameters of the two tasks (Task I and II) and their corresponding statistics. The percentage behind each saccade amplitude window reflects the prevalence of a saccade of that particular amplitude. The distinct analysis of amplitude ranges of more than 15° could not be evaluated reliably, because some participants did not perform sufficient saccades within this domain.

29.7 ± 3.0y; older group (n = 14): mean age 61.6 ± 13.3y; RMSE: younger group (n = 12): mean age 29.5 ± 3.2y; older group (n = 13): mean age 62.2 ± 13.6y; all $p > 0.8$; U-Test). Additionally the effect size of each result was computed using the "Area under the receiver operating characteristic curve" (AUC or A') (Bamber, 1975). Similar to d', AUC can be understood as a measure of overlap of two distributions, with separability being minimal at a value of 0.5 and maximal at 0.0 or 1, respectively (Hentschke and Stüttgen, 2011). The 95% confidence interval for each effect size was calculated analytically (Hanley and McNeil, 1982). Finally, we report Pearson's linear correlation coefficient with the age of the participants for all eye-movement parameters and its corresponding significance level.

RESULTS

Thirty-four participants between the age of 25 to 85 performed two different oculomotor tasks in an indoor environment: (I) walking through a hallway with free gaze and (II) visually tracking a stationary object on the ground while walking straight ahead.

TASK I—WALKING WITH FREE GAZE

Saccade and blink rate

When walking along a hallway with no specific instructions we neither observed a significant difference in walking time between the younger (mean: 26.5 ± 2.7 s) and the older participants (mean: 24.1 ± 4.8 s; $Z = 1.54$; $p = 0.124$; U-test), nor a correlation of walking time and age ($r_{(32)} = -0.260$; $p = 0.138$). Yet, several eye-movement parameters depended on age. The frequency of saccades showed a significantly decrease in the older participants as compared to the younger (**Table 1**) and correlated with age ($r_{(32)} = -0.484$; $p = 0.004$; **Figure 2A**). There was a trend towards an increase in the frequency of eye blinks in older participants, but this trend did not reach statistical significance neither in the median-split analysis (**Table 1**), nor in the correlation analysis ($r_{(32)} = 0.313$; $p = 0.07$; **Figure 2B**).

Parameters of individual saccades (amplitude and velocities)

With respect to the parameters of individual saccades (amplitude and velocity measures), there was a trend towards smaller saccade amplitudes in the older participants, which however, did not reach significance (**Table 1**). Yet, we found a negative correlation between age and median saccade amplitude ($r_{(32)} = -0.396$; $p = 0.02$; **Figure 2C**). When analyzing the amplitudes of horizontal and vertical saccades separately only downward and leftward saccades showed a significant decrease in the older group (**Table 2**). Just as median saccade amplitude, saccade peak and mean velocity were negatively correlated with age (peak-velocity: $r_{(32)} = -0.626$; $p < 0.001$; **Figure 2D**; mean-velocity: $r_{(32)} = -0.567$; $p < 0.001$; **Figure 2E**). For those two parameters the median-split analysis showed a clearly significant decrease in the older population (**Table 1**). This was especially true for saccades in the horizontal direction (**Table 2**) and also trended to be significantly lower in the older group for downward saccades. Yet, upward saccades did not show any statistical differences between groups for either saccade mean- or peak-velocity (**Table 2**). Finally, the saccade distribution for older participants was less skewed, as reflected by the significantly lower median q-value (**Table 1**) and the negative correlation of age with q-value $r_{(32)} = -0.583$; $p < 0.001$; **Figure 2F**). When analyzing the standard deviations of the saccade parameters (amplitude, mean- and peak-velocities and q-value) in relation to the age of the participants, there

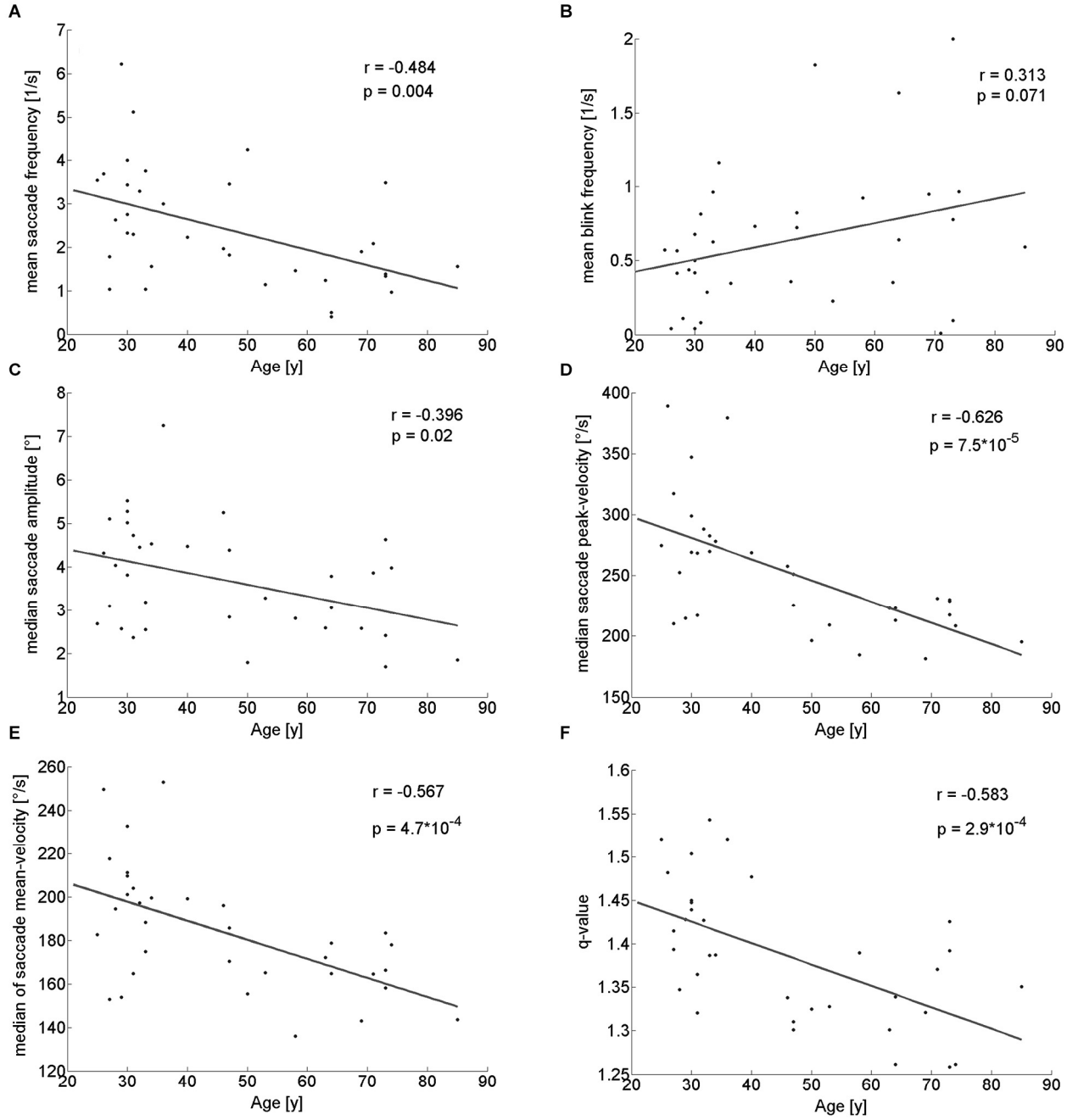

FIGURE 2 | Pearson correlation of different eye movement parameters with participants' age. There is a significant decline with age of saccade frequency **(A)**, saccade amplitude **(C)**, saccade peak- **(D)** and mean-velocity **(E)** and q-value **(F)**. Blink rate trended to be larger in older participants **(B)**.

was a negative correlation for all of them (saccade amplitude: $r_{(32)} = -0.759$; $p < 0.001$; **Figure 3A**; saccade peak-velocity: $r_{(32)} = -0.752$; $p < 0.001$; **Figure 3C**; saccade mean-velocity: $r_{(32)} = -0.731$; $p < 0.001$; **Figure 3E**; q-value: $r_{(32)} = -0.477$; $p = 0.004$; **Figure 3G**). This negative correlation remained for the variation coefficient, which serves as the standardized (normalized) measure of dispersion of the four saccadic performance parameters (saccade amplitude: $r_{(32)} = -0.349$; $p = 0.043$; **Figure 3B**; saccade peak-velocity: $r_{(32)} = -0.460$; $p = 0.006$; **Figure 3D**; saccade mean-velocity: $r_{(32)} = -0.556$; $p < 0.001$; **Figure 3F**; q-value: $r_{(32)} = -0.404$; $p = 0.018$; **Figure 3H**).

Main sequence

Saccade amplitudes and velocities are not independent from each other, but coupled through the so-called main sequence.

Table 2 | Saccade mean- and peak-velocity examined separately for each direction.

	Eye-movement parameter		U-test				
			Young (SD)	Old (SD)	*Z*-value	*p*-value	Effect-size (AUC)
Task I (walking with free gaze)	median saccade amplitude [°] for saccades	Upward	4.39 (1.46)	3.50 (1.69)	1.274	0.203	0.669 [0.484 0.855]
		Downward	5.46 (2.68)	3.79 (1.65)	1.963	0.050	0.699 [0.521 0.877]
		Leftward	7.26 (2.57)	4.40 (1.32)	3.582	0.0003	0.862 [0.734 0.990]
		Rightward	6.66 (2.29)	5.14 (2.21)	1.688	0.092	0.671 [0.489 0.854]
	median saccade mean-velocity [°/s] for saccades	Upward	147.9 (15.4)	139.8 (14.8)	0.861	0.389	0.625 [0.433 0.817]
		Downward	164.9 (32.1)	138.0 (16.9)	2.721	0.007	0.775 [0.616 0.934]
		Leftward	207.9 (41.9)	161.5 (27.2)	3.237	0.001	0.827 [0.685 0.969]
		Rightward	197.1 (32.0)	169.1 (29.3)	2.342	0.019	0.737 [0.568 0.906]
	median saccade peak-velocity [°/s] for saccades	Upward	174.8 (24.5)	170.3 (25.4)	0.241	0.810	0.559 [0.361 0.757]
		Downward	189.1 (45.5)	166.1 (21.2)	1.722	0.090	0.675 [0.493 0.857]
		Leftward	267.0 (55.4)	201.2 (38.2)	3.444	0.0006	0.848 [0.714 0.982]
		Rightward	253.4 (47.2)	199.7 (38.9)	2.961	0.003	0.799 [0.648 0.951]

Median saccade amplitude, mean- and peak-velocity of the two groups during the first task and their corresponding statistics. Only saccades with a higher mean-velocity of more than 100° for each direction were analyzed to exclude saccades with an unspecific direction.

When fitting a power function to the main sequence (see Section Methods) for these amplitude ranges (**Figure 4A**), the exponent of the power function ("L"), showed no significant difference between the groups (**Table 1**) or correlation with age ($r_{(32)} = 0.04$; $p = 0.821$; **Figure 4C**). On the other hand, the fit parameter K, which corresponds to the rise of the power function when the exponent is set, was significantly smaller in older participants (**Table 1**) and negatively correlated with age ($r_{(32)} = -0.476$; $p = 0.004$; **Figure 4B**). In addition, the analysis of saccade peak-velocity within certain amplitude ranges showed a significantly smaller peak-velocity in the older participant group for all analyzed amplitudes (**Table 1**). In sum, nearly all saccade parameters are affected by age, but the general shape of the main sequence remains remarkably unaffected.

Spontaneous tracking

During the free exploration of task I, there were periods in which participants spontaneously tracked a target during walking. These tracking movements had an average gain above 1 for nearly all (29/30) participants. There was no significant linear dependency on age ($r_{(28)} = 0.282$; $p = 0.13$; **Figure 5A**), even though a median-split analysis indicated a somewhat higher gain for the older half of observers (**Table 1**).

TASK II—TRACKING OF A STATIONARY TARGET WHILE WALKING

For the tracking task, we did not find any significant dependence of tracking gain or tracking performance (as quantified by the RMSE) on age (gain: $r_{(26)} = -0.169$; $p = 0.39$; **Figure 5B**; RMSE: $r_{(23)} = 0.064$; $p = 0.76$; **Figure 5C**). Similarly, a median-split analysis did not show any significant difference between the older and the younger half of the participants (**Table 1**).

DISCUSSION

In this study we analyzed the age-dependent changes of basic eye-movement parameters in a real-world setting during everyday tasks. Participants were free to move their eyes and head during self-motion. Some of the oculomotor parameters, such as saccade frequency and velocities, showed a significant decline with healthy aging. Others, i.e., tracking performance of an earth-fixed target during self-motion, did not appear to be influenced by age. Accordingly, our saccade data resemble most findings obtained under laboratory conditions. Our findings concerning smooth eye movements, however, challenge the transferability of eye-movement data from the laboratory to the real world.

WALKING WITH FREE GAZE

In task I, participants had to walk along a hallway with free gaze. A key result was the significant decrease of saccade peak- and mean velocity with age. Previous results on saccade peak velocity in the laboratory were inconsistent and reported both a decline with aging (Warabi et al., 1984; Sharpe and Zackon, 1987; Irving et al., 2006) as well as no significant age dependency (Henriksson et al., 1980; Munoz et al., 1998). While the data of Henriksson et al. (1980) might have had too little statistical power to show a significant effect (6–7 participants per age-group and about 10 saccades for each amplitude investigated), Munoz et al. (1998) investigated only saccades of an amplitude of 20°. Others have hypothesized that an amplitude-dependent saturation in saccade peak velocity in older participants might only affect saccade velocities for amplitudes exceeding 20° (Moschner and Baloh, 1994), which could not be confirmed by our results. The main sequence fit-parameters showed a continuous, significant decline of saccade peak velocity with age.

Mean saccade velocity in the elderly has rarely been examined before. Our results showed a clear reduction for older participants, which was also reported by Spooner et al. (1980) and, with a less strong reduction, by Abel et al. (1983). This effect might be explained by the results of Munoz et al. (1998), who found a significant increase in saccade duration in the oldest participants without an accompanying drop in peak velocity for saccades of the same amplitude. This finding implies a change of saccade skewness with age. Indeed,

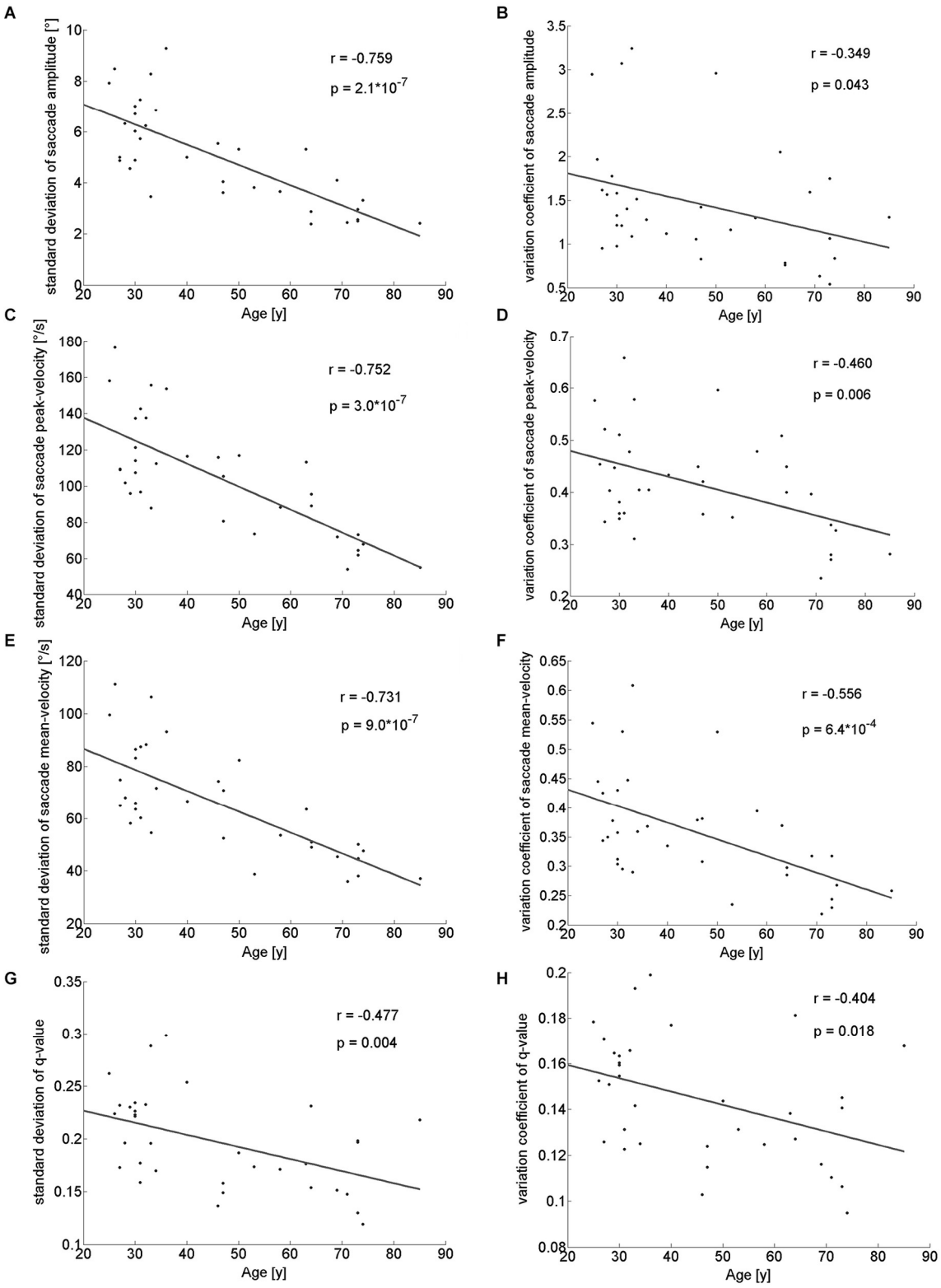

FIGURE 3 | Standard deviations and variation coefficient of saccade amplitude (A,B), peak- (C,D) and mean-velocities (E,F) and q-value (G,H) in relation to the age of the participants. There is a clearly negative correlation for these parameters indicating a decreased variability of saccadic performance in older participants.

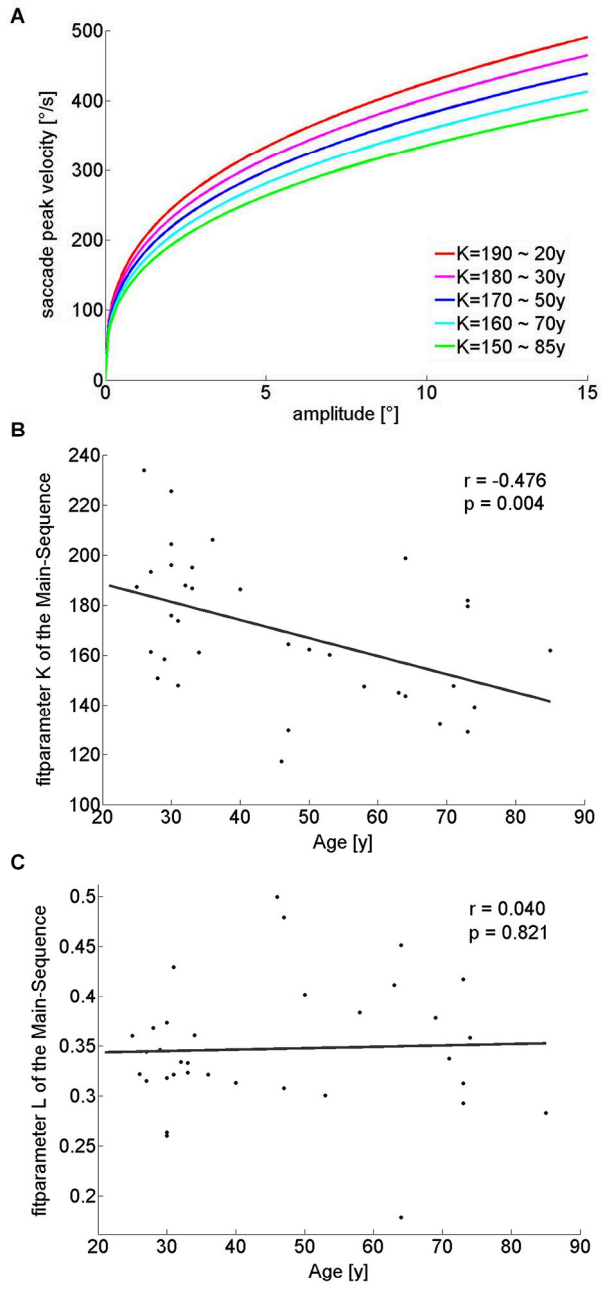

FIGURE 4 | Illustration of Main-sequence power-function fits for different K-values, while the exponent ("L") remains unchanged (A), each K-value relates to a different age cohort, as extracted from the linear regression of K-value over age (B). L-values were constant at 0.35 for all fits **(C)**. With increasing age, smaller K-values **(B)** lead to decreasing slopes of the power functions and therefore smaller saccade peak-velocities for the same amplitudes when L-values are constant **(C)**.

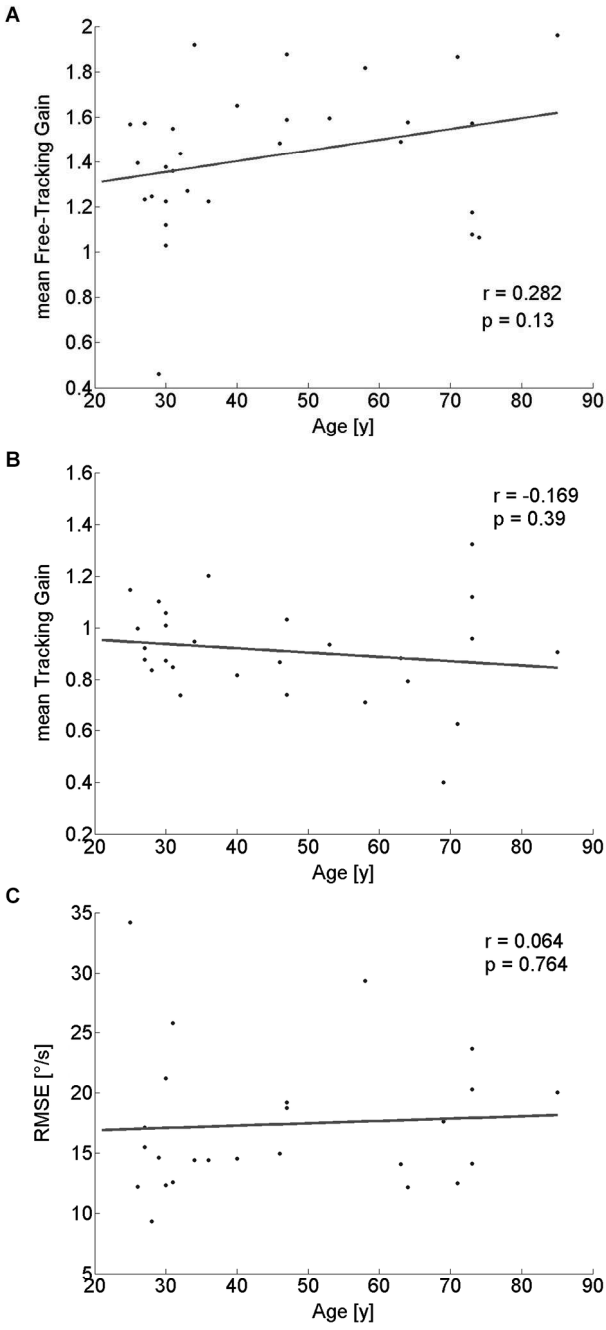

FIGURE 5 | Pearson correlation of tracking-performance parameters with participants' age. Neither tracking gain during free exploration **(A)**, nor gain **(B)** or RMSE **(C)** of the tracking eye-movement of a specific target showed a significant correlation with age.

a generally altered saccade velocity profile of the elderly is also suggested by the q-values as observed in our study. Older participants showed significantly smaller q-values, indicating a less curved saccade velocity profile. This is reflected by a less increased saccade peak-velocity as compared to the saccade mean-velocity.

Another interesting aspect is the separately analyzed age-related difference between horizontal and vertical saccades. For vertical saccades, Huaman and Sharpe (1993) previously reported a decrease in the maximal voluntary excursion in the elderly but no significantly different saccade peak velocity. Our results show a different picture, since saccade amplitude and

mean- and peak-velocities were significantly smaller in the older group especially in the horizontal plane. In contrast, in the vertical domain, only the downward saccades showed a trend for being smaller in older participants. This might be mainly due to the nature of the hallway, in which the ceiling is comparably uninteresting/uninformative, as objects and other potential targets of exploration were mostly present in the horizontal periphery.

The general decrease of saccade speed could be due to a loss of contractibility (McKelvie et al., 1999) or mechanical efficiency (Clark and Demer, 2002) of the eye muscles while aging. Concerning their neural basis, saccade properties are defined by burst neurons in the paramedian pontine reticular formation and are not under voluntary control (Sparks, 2002). The significantly decreased saccade velocities and the smaller q-values for older participants suggest a generally lower activity and a less marked burstiness of these neurons. While the brainstem itself seems to be unaffected by healthy aging (Brody and Vijayashankar, 1977), these neurons receive input from the frontal eye fields, superior colliculus, parietal cortex, and basal ganglia (Wurtz and Goldberg, 1989; Sparks, 2002; Leigh and Zee, 2006). Reduced function in one of these areas or brain regions in older participants could be responsible for a decreased firing frequency of premotor or motor neurons and therefore the reduced saccade velocities. For example, it has been shown that frontal lobe lesions can lead to a slowing of saccades (Sharpe, 1986). Indeed, there are studies suggesting a prefrontal functional (Fabiani and Friedman, 1997) and structural (West, 1996) decline with aging. Additionally some studies showed a decreased neuronal density (Huttenlocher, 1979) and a loss of cortical gray matter in the elderly (Pfefferbaum et al., 1994), which might also contribute to a decrease in saccade velocity.

The reduction of saccade frequency, amplitude and velocities could be attributed to a more narrow viewing area of elderly people. This is in line with the decreased variability of saccadic performance in older participants, as shown by the negative correlation of standard deviation of saccadic parameters with age in our study. Yet, the negative correlation of the variation coefficient with age shows, that saccade performance is in general less variable in the elderly. A more narrow viewing area in the elderly is also supported by our results on the separately analyzed horizontal and vertical saccades, which show a consistent decrease in saccade amplitude and velocities in the older group, especially for saccades in the horizontal plane. This might be due to higher effort while walking, e.g., more looking on the pathway to avoid obstacles and plan appropriate motor responses (Di Fabio et al., 2003; 't Hart and Einhäuser, 2012), or less confidence in exploring while walking due to a higher likelihood and cost of a potential fall (Hadley et al., 1985). This is in line with the structure of the hallway, in which exploration targets were mostly present in the horizontal periphery. Since objects are the dominant driver of fixations (Stoll et al., 2015), less exploration might be the main reason for the significantly decreased horizontal saccade amplitudes and velocities in the older participants. Chapman and Hollands (2006) have shown that older adults looked significantly earlier to targets, and fixated the targets for longer periods than younger adults while walking along a pathway. The authors explained their result as a consequence of age-related decline in general visual function (Morgan, 1993), slowed cognitive processing (Salthouse, 1996) and decline in visuomotor processing (Moschner and Baloh, 1994).

TRACKING EYE-MOVEMENTS DURING SELF-MOTION

In our study, the performance of tracking eye-movements while walking showed different results for spontaneous tracking movements (task I) as compared to instructed tracking movements (task II). Active tracking of optic flow elements in the laboratory has been reported to have a gain close to perfect, i.e., 1.0 (Niemann et al., 1999), which was also the case in our study during tracking of a given stationary target. On the other hand, the gain of most participants during spontaneous tracking was greater than 1.0. This result could be due to the fact that objects in the real world, unlike most artificial stimuli and the target used in our study, have a considerable extent. This leads to more eye movements across the object during the tracking and eventually to a higher speed of the eye during tracking. On the other hand, the computation of optic flow fields of real world scenes can be imprecise because of light reflections or plain surfaces (Gautama and Van Hulle, 2002). This might have led to an underestimation of target velocity in this task. Nevertheless, a median-split analysis showed that the gain of the group of older participants was significantly higher as compared to the younger participants. This suggests a generally more imprecise tracking eye-movement of freely-chosen targets during walking in the elderly. One possible explanation could be an age-related, gradually functional decline of the visual-vestibular system. It has been shown in the laboratory that visual influences on the vestibulo-ocular reflex decline in the elderly together with a deterioration of visual following (Paige, 1994). Accordingly, tracking eye-movements in the elderly might get affected due to differing available input signals.

Unlike smooth pursuit in the laboratory, which has been shown to get worse in the elderly as compared to younger adults (Moschner and Baloh, 1994; Ross et al., 1999), visual tracking performance of a given target during self-motion appeared to be unaffected by age in our study. This finding might suggest compensatory mechanisms, e.g., head movements, or additional sensory cues like optic flow or vestibular signals, which help to maintain normal performance. Paige (1994) found an increased likelihood and intensity of circular vection, a psychophysical measure of visual-vestibular interactions, and proposed an enhanced perception of self-motion in the elderly, which might serve as a visual compensation for age-dependent loss of vestibular cues. Accordingly, optic flow information could neuronally be given a stronger weight in the process of eye-movement control during self-motion. Such an enhanced weight of sensory self-motion information could explain the decreased smooth-pursuit gain in the laboratory due to its absence when measuring with a restrained head. On the other hand motion perception and detection of random dot patterns in the laboratory have been shown to deteriorate in the elderly (Tran et al., 1998). Along similar lines, Billino et al. (2008)

showed a gradual decrease in the perception of two-dimensional translational motion and biological motion in the elderly. In contrast, heading detection via expanding radial flow fields was stable across the lifespan in this study (Billino et al., 2008). Nevertheless, a recent study of Lich and Bremmer (2014) showed a decreased absolute heading performance in the elderly in a virtual-reality setting. In this study, the authors were able to model their results in a neural network of visual self-motion processing by an age related neuronal cell loss in area MST. Taken together, this suggests an impairment of motion-selective areas in the brain, such as the middle temporal (MT) area (Newsome and Paré, 1988), the MST area (Duffy and Wurtz, 1991; Bremmer et al., 1999) and the VIP area, which is particularly important in decoding global motion and heading information (Bremmer et al., 2002a; Bremmer, 2005; Chen et al., 2011).

The suggested relevance of self-motion processing for oculomotor performance in the real world as compared to laboratory settings is supported by studies in schizophrenia patients. These patients show an impaired smooth pursuit in the laboratory (Holzman et al., 1974; O'Driscoll and Callahan, 2008) but only a subtle change of tracking eye-movement performance in the real world (Dowiasch et al., 2014). The importance of additional sensory signals to the visual system of schizophrenia patients has been shown by a study of Holzman (2000), in which patients performed worse in a velocity discrimination task when additional non-velocity stimulus cues were eliminated. In natural behavior, these additional cues are almost always present and might serve as a support or even substitute to compensate impairments of specific visual functions. The tracking of a moving object in a real-world situation, while participants are not moving but able to move their head, is an interesting issue for future research. Such a paradigm might be more closely linked to smooth pursuit in the laboratory and therefore might bridge the gap between the results in the literature and the real-world data in our study.

Being aware of the numerous differences between our real-world tasks and typical laboratory measurements, our results provide a first step towards analyzing real-world oculomotor behavior in healthy aging. Furthermore, our correlation analysis together with the effect sizes allowed us to examine to what extent age influences different eye-movement parameters in real-world situations. Together with two recently published studies (Marx et al., 2012; Dowiasch et al., 2014) our results highlight the possible advantages of mobile eye tracking as a fast, reliable, objective and easy-to-use tool, especially when investigating clinical populations or the elderly. Identifying the sources of differences and commonalities between laboratory results and real-world data will be an important issue for future research. Especially the multimodal area VIP (Bremmer et al., 2002b; Schlack et al., 2005), for which a functional equivalent has been identified in humans (Bremmer et al., 2001), might play a crucial role in natural contexts by providing and combining additional sensory information. How such key areas in motion processing are related to the changing oculomotor behavior during aging, and how they integrate the rich information available in the real world for gaze control remains an exciting topic for further research. In any case, our present study underlines the need for addressing real-world situations to fully understand the impact of neuronal changes on oculomotor function and motor behavior in general during healthy aging.

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Validation of mobile eye-tracking as novel and efficient means for differentiating progressive supranuclear palsy from Parkinson's disease

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Background: The decreased ability to carry out vertical saccades is a key symptom of Progressive Supranuclear Palsy (PSP). Objective measurement devices can help to reliably detect subtle eye movement disturbances to improve sensitivity and specificity of the clinical diagnosis. The present study aims at transferring findings from restricted stationary video-oculography (VOG) to a wearable head-mounted device, which can be readily applied in clinical practice. **Methods:** We investigated the eye movements in 10 possible or probable PSP patients, 11 Parkinson's disease (PD) patients, and 10 age-matched healthy controls (HCs) using a mobile, gaze-driven video camera setup (EyeSeeCam). Ocular movements were analyzed during a standardized fixation protocol and in an unrestricted real-life scenario while walking along a corridor. **Results:** The EyeSeeCam detected prominent impairment of both saccade velocity and amplitude in PSP patients, differentiating them from PD and HCs. Differences were particularly evident for saccades in the vertical plane, and stronger for saccades than for other eye movements. Differences were more pronounced during the standardized protocol than in the real-life scenario. **Conclusions:** Combined analysis of saccade velocity and saccade amplitude during the fixation protocol with the EyeSeeCam provides a simple, rapid (<20 s), and reliable tool to differentiate clinically established PSP patients from PD and HCs. As such, our findings prepare the ground for using wearable eye-tracking in patients with uncertain diagnoses.

Keywords: progressive supranuclear palsy, mobile eye-tracking, eye movements, Parkinson's disease, video-oculography

INTRODUCTION

Eye movement abnormalities are an essential clinical feature of Progressive Supranuclear Palsy (PSP). Vertical supranuclear gaze palsy or decreased velocities of vertical saccades are a key to the clinical diagnosis of PSP (Litvan et al., 1996). Besides their role as diagnostic signs, eye movement abnormalities disable PSP patients in their daily routine.

Stationary video-oculography (VOG) during head-fixed viewing shows that virtually all forms of eye movements are affected in PSP, with saccadic eye movements being most prominently impaired. Particularly vertical saccades show reduced amplitude and peak velocity when compared to Parkinson's disease (PD) patients and healthy controls (HCs) (Pinkhardt et al., 2008; Chen et al., 2010; Pinkhardt and Kassubek, 2011). Vergence movements and the associated modulation of the linear vestibuloocular reflex are also considerably affected (Chen et al., 2010). The presence of horizontal square wave jerks during attempted fixation of stationary targets is characteristic of PSP (Chen et al., 2010; Otero-Millan et al., 2011). Among these deficits, saccadic peak velocity in the vertical plane shows the sharpest contrast between PSP and PD (Pinkhardt and Kassubek, 2011).

These PSP-specific eye movement abnormalities make clinical investigation of eye movements in patients with Parkinsonian syndromes of great value for differential diagnosis. Correct diagnosis of PSP remains challenging, especially in its early stages (Burn and Lees, 2002). Eye movement abnormalities are not always easy to detect clinically. Particularly, slowing of saccades is a characteristic symptom that can be missed by less experienced neurologists.

Objective measurement devices aid detection of subtle eye movement disturbances. Stationary VOG setups typically require careful calibration, need patient collaboration, and are thus largely impractical for clinical routine. Head-fixed viewing lacks vestibular and other cross-modal information, leaving the relevance of observed eye movement impairment for real-life behavior open. As a first step toward the development of an

objective, easy-to-use method for eye movement-based diagnosis, we here tested if recording eye movements with the versatile, head-mounted EyeSeeCam (Brandt et al., 2006; Schneider et al., 2006, 2009) in a brief and simple fixation protocol can differentiate between patients with clinically established PSP as compared to established PD and HCs, and measured gaze in these groups during free behavior. We aimed at establishing the EyeSeeCam's usage in PD and PSP cases and validating its discriminative power between these groups. The parameters established in the present study in clinically established patients shall pave the way for prospective studies with uncertain diagnoses.

MATERIALS AND METHODS

PARTICIPANTS

Patients examined in the Department of Neurology of the University of Marburg qualified for participation in the study, if they had clinically possible or probable PSP (Litvan et al., 1996) and were not more advanced than Hoehn and Yahr stage IV (Golbe and Ohman-Strickland, 2007). As defined by the NINDS-SPSP criteria (Litvan et al., 1996), all patients had supranuclear gaze palsy or slowing of vertical saccades at the time of examination, as evidenced by an examiner specialized in the clinical evaluation of ocular movements.

As controls, we included patients with clinically probable PD (Gibb and Lees, 1988) and HCs. HCs were free of neurologic, systemic, or psychiatric diseases, including alcohol or substance abuse, as verified by detailed evaluation of their medical histories and a comprehensive physical examination.

Further exclusion criteria were other neurological disorders, dementia (mini mental status examination <24), presently active psychiatric disorder (e.g., depression or psychosis), structural brain lesion (e.g., brain surgery, stroke with persistent neurological deficit), cataract, or other neuro-ophthalmological disorders leading to functionally relevant impairment. Since glasses cannot be worn with the EyeSeeCam, people requiring visual correction by glasses stronger than ±2 dpt were also excluded.

Before inclusion into the study, participants gave their informed written consent. All procedures conformed to the Declaration of Helsinki and were approved by the local ethics committee (Ethikkommission FB20, Philipps-Universität Marburg).

EYE AND HEAD MOVEMENT RECORDINGS

We used a mobile VOG setup (EyeSeeCam) to record the participants' eye and head movements. Participants accustomed themselves to wearing the device, while the experimental procedure was explained.

The head-mounted device consists of a head-fixed camera to record the perspective of the head, two high-speed cameras tracking eye-in-head movements, and a camera, which is automatically aligned with the observer's direction of gaze. Gaze- and head-centered videos are recorded at 25 Hz (**Figure 1A**; Movie 1 in supplementary material); eye movements at 300 Hz.

According to manufacturer's specifications, the spatial resolution of the eye-tracking device is given to 0.02° and the precision

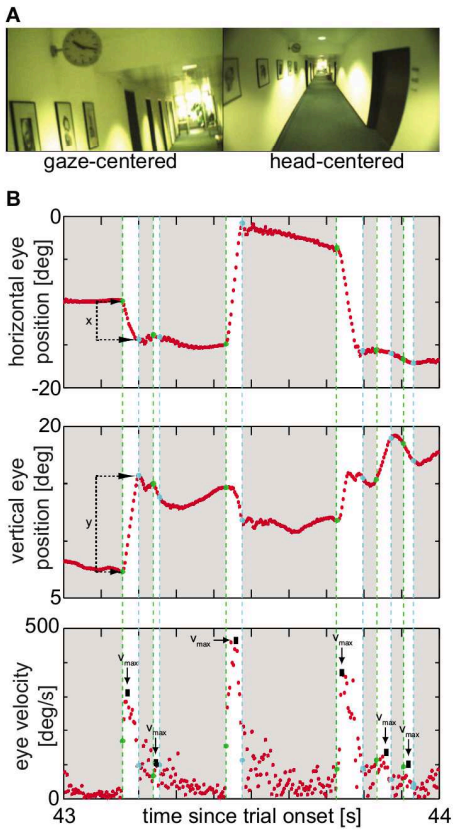

FIGURE 1 | (A) Example frame at 43.81 s in the real-life measurement, while a PD patient was looking at the clock; left: gaze camera, right: head camera. The movie of this scene including velocity histograms is shown as supplemental online Movie 1. **(B)** Eye-traces of the scene. Upper panel: Horizontal eye position, indicating the horizontal amplitude of saccades; starting and end points of saccades are marked by green and cyan dashes lines, respectively; durations of saccades are highlighted by a white background. Middle panel: Vertical eye position, indicating the vertical amplitude of the same saccades. Lower panel: Absolute eye velocity, arrows mark saccade peak velocities, used for analysis.

(relative error) on the order of 0.1° ("maximal resolution error," Schneider et al., 2009). The accuracy (absolute error) of the device under ideal conditions is about 0.5° according to specifications, and can substantially worsen if the goggles move relative to the head during prolonged measurements without recalibration. Hence, all analysis reported here only use relative measures, which are unaffected by these drifts, such as velocities and saccade amplitudes.

Being not concerned with absolute gaze orientation (i.e., with high accuracy) comes at the advantage that the device may be operated using an internal ("default") model of ocular geometry for all participants. In this mode of operation, the mapping from eye measurements on gaze direction does not require a subject-specific calibration, which is in particular beneficial in patients with limited ocular motor control or limited compliance with instructions. Although this sacrifices some precision (depending on the actual head shape compared to the default

model), no systematic effect on the measures analyzed here can be expected. For the "fixation protocol" (see below), the default model was used in all participants; for the "real-life measurements" (see below), in those participants, in whom it was possible, the subject-specific model obtained from the fixation protocol was used; for the remainder the default model was also used in real-life measurements. Since the subject-specific adaptation of the model represents a calibration procedure for absolute position, for the real-life measurement, these participants will be referred to as successfully and unsuccessfully calibrated, respectively.

When extracting head movements from the head fixed camera, for the analysis conducted here, the spatial resolution is limited by the pixel width of about 0.3°, even though sub-pixel analysis would be possible in principle. When analysis is based on subsequent frames, this limits the resolution for head movements to about 7.5°/s. While integration over multiple frames would be possible to lower this number, this would come at the cost of lower temporal resolution and thus possibly lumping distinct head movements into one.

Fixation protocol

To test the utility of the EyeSeeCam as diagnostic tool, we employed a "fixation protocol." In addition to being the first experimental part, this protocol also served to refine the EyeSeeCam's calibration for the subsequent real-life experiments by adapting the system's internal eye model to the individual. During the fixation protocol, the participants' heads were unrestrained, but they were asked to avoid head movements as far as possible. They were instructed to move their eyes to look successively at 5 laser dots projected onto a wall straight ahead, a central dot and four at 8.5° in the cardinal directions. An experimenter pointed with a finger at the dot the participant should look at. To give the participant the possibility to self-pace their fixations, presentation of the dots in time was to some degree flexible and not exactly clocked. However, the participant had to look at each dot for 2 s at least once in a time span of approximately 20 s. While this procedure is far less constrained and standardized than usual laboratory measurements, it is still more controlled than the real-life conditions of the present study. This flexible and efficient procedure makes the participation of very severely affected patients possible, presenting a clear advantage over more constrained settings.

Real-life behavior

For measuring a large range of gaze behaviors as occurring in real-life situations, we asked participants to perform a series of tasks, while spontaneous eye and head movements were recorded. First, free-exploration behavior was assessed by asking participants to walk along a 50 m corridor. Right before the participant turned around at the end of the corridor, an experimenter laid two paper spots on the floor to assess tracking behavior. Participants were asked to track the dots with their eyes, while walking back toward them. Finally, participants took the elevator and descended one-level to test a situation without active movement in a confined visual environment with subtle vestibular input. Those two PSP and PD patients who were wheelchair-dependent were wheeled throughout the whole procedure by an experimenter instead of actively walking.

The objective of the real-life measurement was to provide a naturalistic set of behaviors, while differences between real-life conditions were not at the focus of the current study. Consequently, all data of real-life measurement were pooled per participant. The real-life measurement lasted less than 10 min per participant.

DATA ANALYSIS AND STATISTICAL EVALUATION

Eye movements

Raw eye-position data were processed offline using MATLAB (Matlab 7.10, The MathWorks, Natick, MA), which was also used for statistical analysis. We calculated eye velocity by differentiation of the horizontal and vertical eye position (**Figure 1B**). Absolute speed was then calculated as the square root of the sum of the squared horizontal and squared vertical velocity componentss.

All phases faster than 60°/s and lasting longer than 10 ms are referred to as "saccades," irrespective of whether they were actual saccades or fast phases of reflexive movements (**Figure 1B**). This threshold is higher than those typically used in laboratory settings, as signals obtained during real-life measurements contain rich eye movement dynamics and are typically noisier than under constrained settings. The conservative choice is, however, consistent with previous research on eye movements in PSP patients: for example, judging from the figures in Pinkhardt et al. (2008), their patients had their 5% percentile of peak saccade velocities around or above 60°/s, meaning that we can still expect to include about 95% of actual saccades with our comparably conservative criterion. Since this criterion could also be employed in practice, it will not affect any conclusion on the discriminability of patient groups. Nonetheless, for the general questions pertaining to eye movement disturbances in PSP and PD, the fact that any threshold must remain arbitrary motivates to add an analysis that does not classify eye movements in saccade/non-saccade, but uses the unclassified (i.e., raw) eye movement data (see below and section "Unclassified Eye Movements").

Parameters to describe saccades were their direction, peak velocity, amplitude, and duration (**Figure 1B**). Since peak velocity, saccade amplitude, and duration are typically not independent, the functional relationship of amplitude and peak velocity and of amplitude and saccade duration, the so-called main sequence (Bahill et al., 1975), was also considered for real-life data: we fitted the relation with a power function of the form velocity $= a \times \text{amplitude}^b$ or duration $= a \times \text{amplitude}^b$, respectively (cf. Garbutt et al., 2003), and considered only the fit parameters a and b further. Since reliable fits of main sequences require substantial amounts of data, this analysis was only performed for the real-life measurements.

To test whether there is an abundance of one saccade direction in a group, we coarsely classified saccades into equally spaced 45° wedges: horizontal (±22.5° from the horizontal), vertical (±22.5° from the vertical), and oblique (the remaining $4 \times 45° = 180°$).

For analysis of raw ("unclassified") eye data (i.e., all data irrespective of whether defined as saccade or not),

two-dimensional histograms were used. Each bin of the histograms used for analysis corresponds to a velocity interval of 15°/s in each direction (horizontal and vertical); the central bin ranges from −7.5°/s to +7.5°/s in each direction. The number of samples in each bin is color-coded.

Head movements

Head movements were computed from the video of the head-fixed camera at 25 Hz. To obtain head position, the same stationary point of the environment was marked in each video-frame. From this point's position in the camera's field of view relative head orientation in the world was computed. Head velocity was obtained by differentiation of this signal, and was thus independent of this choice of origin. All quantitative analysis was therefore based on velocities. Unlike for eye movements and due to the low spatial and temporal resolution (section "Eye and Head Movement Recordings" top), we could not classify head movements in distinct classes (e.g., fast/slow) with the data at hand. Therefore, all analysis was based on overall velocity distributions for each individual.

Statistical analysis

Data are presented as mean ± standard deviation. Statistical evaluation used non-parametric tests for raw eye data, such as amplitude and peak velocity of each saccade (Kruskal–Wallis when three groups were compared and Mann–Whitney-*U*-Test for two groups). To compare these parameters in an exploratory manner across participants, the individual distributions are described by their medians as robust measure (since the distributions are either leptokurtic or prone to outliers). Since these medians can be assumed to follow a normal distribution across participants, the group effects were analyzed by parametric tests; that is, ANOVAs for three group comparisons and two-tailed *t*-tests for two-group comparisons and *post-hoc* tests.

Signal-detection-theory measures

For assessing the performance of the classifiers between PSP and PD patients, we performed signal-detection analysis by computing the Receiver-Operating-Characteristic (ROC). The ROC is quantified by its area under the curve (AUC), the cut-off point for maximal specificity and sensitivity, and the corresponding values of specificity and sensitivity. Values are reported such that all values of patients classified as PSP patients are strictly smaller than this cut-off value.

RESULTS

PARTICIPANT CHARACTERISTICS

We investigated 10 PSP patients (6 probable, 4 possible), 11 PD patients and 10 HCs (**Table 1**). All patients were under treatment in the University Hospital in Marburg. There were no significant differences regarding age, disease duration, and gender between the groups. For all patients Hoehn and Yahr stage was assessed in off-state and, as expected, the stages differed significantly between PSP and PD patients (**Table 1**).

Eye velocities and relative eye positions (e.g., saccade amplitudes) require only minimal subject–specific adjustment

Table 1 | Clinical characteristics of the participants in this study: overview.

	PSP	PD	HC
N	10	11	10
Age (years)	65.9 ± 4.6	65.5 ± 12.7	68.3 ± 9.1
Gender (F/M)	3/7	3/8	6/4
DD (years)	3.9 ± 2.7	6.2 ± 4.7	–
H&Y	3.9 ± 0.4	2.5 ± 0.4	
Wheelchair	2/10	2/11	0/10
Real-life measurement time	304.3 ± 114.4 s	242.2 ± 78.5 s	202.8 ± 35.3 s

Details

Patient ID/gender/age [years]	Onset	Exam. date	H&Y	Medication
PSP01/F/67	2004	08/2010	4	Levodopa
PSP02/M/70	2008	08/2010	3	Amantadine
PSP03/F/63	2007	08/2010	4	Levodopa, Amantadine
PSP04/M/70	2007	08/2010	4	Levodopa, Amantadine, Piribedil
PSP05/F/65	2007	08/2010	3	Amantadine, Rotigotine
PSP06/M/67	2000	08/2010	4	Levodopa
PSP07/M/62	2008	02/2011	4	Levodopa
PSP08/M/74	2005	05/2011	4	Levodopa, Amantadine
PSP09/M/59	2010	10/2011	3	Levodopa
PSP10/M/62	2009	11/2011	3	Levodopa
PD01/M/61	2007	09/2010	2	Rotigotine
PD02/M/75	1995	09/2010	3	Levodopa
PD03/M/75	2007	02/2011	1	Ropinirole
PD04/M/64	2000	07/2011	3	Levodopa, Amantadine, Pramipexole, Rasagiline
PD05/M/67	2007	07/2011	1	Levodopa, Ropinirole, Rasagiline
PD06/M/51	2010	09/2011	2	Levodopa, Rasagiline
PD07/F/62	2007	10/2011	3	Levodopa, Rasagiline, Piribedil
PD08/M/38	2010	10/2011	2	Pramipexole
PD09/M/78	2007	12/2011	3	Levodopa
PD10/F/82	2001	12/2011	3	Levodopa, Amantadine, Ropinirole
PD11/F/68	2000	12/2011	3	Levodopa, Amantadine, Pramipexole
HC01/F/58		08/2010		
HC02/M/71		08/2010		

(Continued)

Table 1 | Continued

Patient ID/gender/age [years]	Onset	Exam. date	H&Y	Medication
HC03/F/53		02/2011		
HC04/F/63		02/2011		
HC05/M/73		03/2011		
HC06/F/64		03/2011		
HC07/F/69		03/2011		
HC08/F/74		09/2011		
HC09/M/85		12/2011		
HC10/M/73		12/2011		

PSP, progressive supranuclear palsy; PD, Parkinson's disease; HC, healthy controls; DD, disease duration; H&Y, Hoehn and Yahr Stage. H&Y stage is significantly different between PD and PSP [$t_{(19)} = 4.12$, $p < 0.001$]; real-life measurement duration differs significantly between PSP and HC ($p = 0.02$ post-hoc test); all other comparisons do not show a significant difference ($p > 0.05$).

and could thus be measured accurately in all participants. However, individual-specific calibration of absolute eye-position failed in eight PSP and two PD patients as a consequence of their inability to steadily fixate instructed targets over a 2-s integration window. Interestingly, this inability did not primarily result from square-wave jerks, which were robustly observed only in 1 out of the 10 PSP patients under our experimental conditions. As a consequence of the calibration failures for absolute position, all quantitative analysis hereafter is based on relative eye-position and velocities only.

SACCADES

Fixation protocol

All participants performed a standard fixation protocol, as described in the "Materials and Methods" section, which was also used for individual calibration refinement. Irrespective of whether this absolute-position calibration was successful or not, these measurements provided a sufficient number of visually-guided saccades to analyze differences between PSP patients and PD patients or HCs (**Figure 2**).

Averaged median saccadic peak velocity was $135.1 \pm 43.8°$/s for PSP, $220.1 \pm 31.5°$/s for PD patients and $233.0 \pm 44.4°$/s for HCs. A One-Way ANOVA revealed a significant main effect [$F_{(2,\ 28)} = 17.81$, $p < 0.001$, **Figure 2B**] and *post-hoc t*-tests showed that PSP patients generated saccades with significantly slower median peak velocity than PD patients [$t_{(19)} = 5.14$, $p < 0.001$] and HCs [$t_{(18)} = 4.96$, $p < 0.001$]. There were also significant differences in the vertical components of saccade peak velocity. Averaged vertical saccade peak velocity was $54.9 \pm 28.0°$/s for PSP patients, $158.5 \pm 47.9°$/s for PD patients and $151.1 \pm 60.3°$/s for HCs [$F_{(2,\ 28)} = 14.53$, $p < 0.001$; PSP-PD: $t_{(19)} = 5.83$, $p < 0.001$; PSP-HC: $t_{(18)} = 4.51$, $p < 0.001$, **Figure 2C**].

Saccade amplitudes also differed significantly between groups [$F_{(2,\ 28)} = 18.26$, $p < 0.001$, PSP-PD: $t_{(19)} = 4.26$, $p < 0.001$, PSP-HC: $t_{(18)} = 6.60$, $p < 0.001$, **Figure 2B**]. Averaged median amplitudes were $1.88 \pm 0.72°$ for PSP patients, $4.16 \pm 1.53°$ for PD patients and $5.42 \pm 1.53°$ for HCs. Vertical saccade amplitude was $0.52 \pm 0.37°$ for PSP patients, $2.89 \pm 1.62°$ for PD patients and $3.03 \pm 2.16°$ for HCs and thus also differed significantly [$F_{(2,\ 28)} = 7.76$, $p = 0.002$; PSP-PD: $t_{(19)} = 4.37$, $p < 0.001$; PSP-HC: $t_{(18)} = 3.57$, $p = 0.002$, **Figure 2C**].

We did not find significant main effects for the horizontal components of peak velocity [$F_{(2,\ 28)} = 2.12$, $p = 0.14$, ANOVA; **Figure 2D**] and amplitude [$F_{(2,\ 28)} = 1.69$, $p = 0.20$, **Figure 2D**].

The ROC comparing saccade peak velocity of PSP and PD patients showed an AUC of 0.95. Specificity was 11/11 and sensitivity was 9/10 for a cut-off value of 189.8°/s (i.e., all patients having slower peak velocities than this value were classified as PSP) patients. For the comparison of vertical saccade peak velocities, the AUC was 1 and for the cut-off value 111.7°/s, specificity was 11/11 and sensitivity was 10/10. The AUC for the comparison of saccade amplitude was 0.97 with a specificity of 11/11 and a sensitivity of 9/10 for a cut-off value of 2.79°. For the vertical component, AUC was 0.99 and the ROC analysis showed a specificity of 10/11 and a sensitivity of 10/10 for the cut-off value 1.68°.

For completeness, we also analyzed saccade duration in all groups. We found a significant main effect between groups [PSP: 19.6 ± 7.2 ms, PD: 26.2 ± 6.3 ms, HC: 32.7 ± 6.5 ms, $F_{(2,\ 28)} = 9.6$, $p < 0.001$, see **Figures 2E,F**]. *Post-hoc t*-test revealed significant differences between all groups [PSP-PD: $t_{(19)} = 2.25$, $p = 0.037$; PSP-HC: $t_{(18)} = 4.27$, $p < 0.001$; PD-HC: $t_{(19)} = 2.30$, $p = 0.033$]. Sensitivity was 7/10 and specificity was 9/11 for the cut-off value 21.6 ms, the AUC was 0.77. These values are much lower than for amplitude and peak velocity and thus less informative where differential diagnosis is concerned. Hence, we hereafter focus most analysis on peak velocity and amplitude.

Real-life

Since the eye movement impairment in PSP was evident during the fixation protocol, we next analyzed their relevance for real-life situations. Hence, we measured the spontaneous ocular motor behavior in a real-life, minimally restrained scenario, comprising self-paced walking in a corridor, tracking of a stationary target, and taking an elevator. Self-paced walking implies speed differences between participants. ANOVA revealed a significant main effect for differences in real-life measurement duration [$F_{(2,\ 28)} = 3.85$, $p = 0.03$, **Table 1**]; the difference was not significant between PSP and PD patients, but for HCs the measurement lasted significantly shorter than for PSP patients [$t_{(18)} = 2.68$, $p = 0.02$]. Aggregating over the whole real-life measurement, we assessed the same parameters as during the fixation protocol (**Figure 3**).

All groups had the same fraction of vertical [PSP: $24.1\% \pm 15.4\%$, PD: $28.9\% \pm 10.4\%$, HC: $31.7\% \pm 7.1\%$, $F_{(2,\ 28)} = 1.14$, $p = 0.33$], horizontal [PSP: $21.7\% \pm 9.0\%$, PD: $18.5\% \pm 8.1\%$, HC: $18.3\% \pm 5.9\%$, $F_{(2,\ 28)} = 0.64$, $p = 0.53$] and oblique [PSP: $54.3\% \pm 10.1\%$, PD: $52.6\% \pm 6.1\%$, HC: $50.0\% \pm 3.7\%$, $F_{(2,\ 28)} = 0.92$, $p = 0.41$] saccades.

The medians of saccade peak velocity differed significantly between the groups [$F_{(2,\ 28)} = 5.47$, $p = 0.01$, **Figure 3B**]. PSP

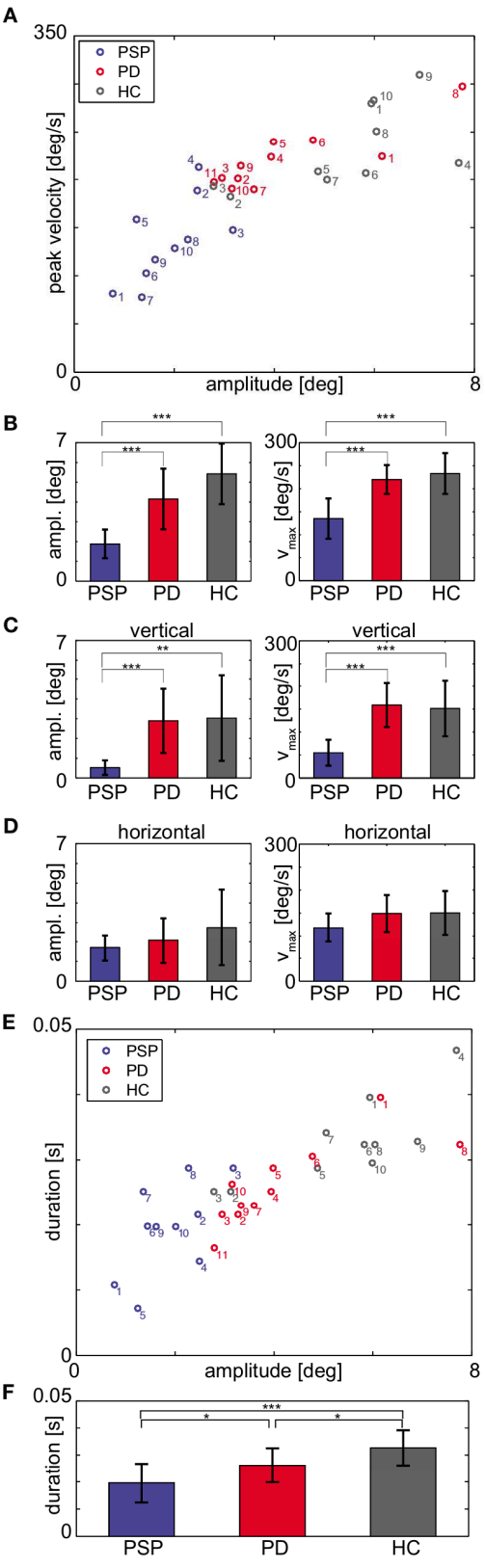

FIGURE 2 | Continued

FIGURE 2 | (A) Medians of saccade peak velocity and amplitude for each participant during the fixation protocol. **(B)** Mean over participants of median amplitude (left panel) and median peak velocity (right panel) for each group. **(C)** Vertical component and **(D)** horizontal component of the data of panel **(B)**; **(E)** Medians of saccade duration and amplitude for each participant during fixation protocol; note that the duration is discretized due to sampling frequency **(F)**. Mean over participants of median duration. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

patients' averaged median saccade peak velocity was 131.1 ± 29.0°/s and thus slower than those of PD patients [163.1 ± 25.8°/s; $t_{(19)} = 2.68$, $p = 0.002$] and HCs [160.2 ± 15.4°/s; $t_{(18)} = 2.80$, $p = 0.01$]. The vertical component of saccade peak velocity (PSP: 71.9 ± 15.5°/s, PD: 89.6 ± 11.5°/s, HC: 89.5 ± 9.6°/s) also differed significantly [$F_{(2,\ 28)} = 6.88$, $p = 0.004$, PSP-PD: $t_{(19)} = 3.00$, $p = 0.007$; PSP-HC: $t_{(18)} = 3.05$, $p = 0.007$, **Figure 3C**], whereas there was no significant difference between means of the horizontal component of peak velocity [$F_{(2,\ 28)} = 1.66$, $p = 0.21$, **Figure 3D**] between groups.

ANOVA did not reveal a significant main effect for saccade amplitude [$F_{(2,\ 28)} = 2.55$, $p = 0.10$, **Figure 3B**], but the vertical component of saccade amplitude differed significantly [$F_{(2,\ 28)} = 3.46$, $p = 0.045$, **Figure 3C**]; *post-hoc t*-tests revealed that PSP patients' vertical component of saccade amplitude was significantly shorter (0.79 ± 0.36°) than PD patients' [1.12 ± 0.33°; $t_{(19)} = 2.12$, $p = 0.047$] and HCs' [1.06 ± 0.13°; $t_{(18)} = 2.16$, $p = 0.04$]. There was no significant difference between medians of the horizontal components of amplitudes [$F_{(2,\ 28)} = 0.25$, $p = 0.78$, **Figure 3D**].

The AUC was 0.84 for peak velocity with a sensitivity of 8/10 and a specificity of 9/11 for the cut-off value 139.9°/s. For vertical peak velocity, the AUC was 0.82 and for a cut-off value of 83.2°/s sensitivity was 7/10 and specificity was 8/11. For analysis of saccade amplitudes, the AUC was 0.80 with a sensitivity of 8/10 and a specificity of 8/11 for a cut-off value of 1.85°. The AUC for comparison of vertical components was 0.75 with a sensitivity of 6/10 and a specificity of 11/11 for the cut-off value 0.69°.

Differences in medians of saccade duration were not significantly different between groups [PSP: 25.5 ± 3.7 ms, PD: 27.6 ± 4.0 ms, HC: 25.6 ± 2.3 ms, $F_{(2,\ 28)} = 1.31$, $p = 0.29$; see **Figures 3E,F**].

Correlation between fixation protocol and real-life

Median of peak velocity and its vertical component in the fixation protocol and during real-life measurement correlated significantly ($N = 31$, $r = 0.39$, $p = 0.03$; vertical: $r = 0.50$, $p = 0.004$). Thus, the data collected during the fixation protocol not only differentiated between PSP and PD patients, but also in part predicted real-life performance.

Main-sequence analysis

Peak velocity and duration were plotted as a function of amplitude for each saccade of every participant. We fitted this main sequence with a power function (**Figure 4A**) and compared the fit parameters between groups. There were no significant differences between groups with respect to the value of fit parameters *a*

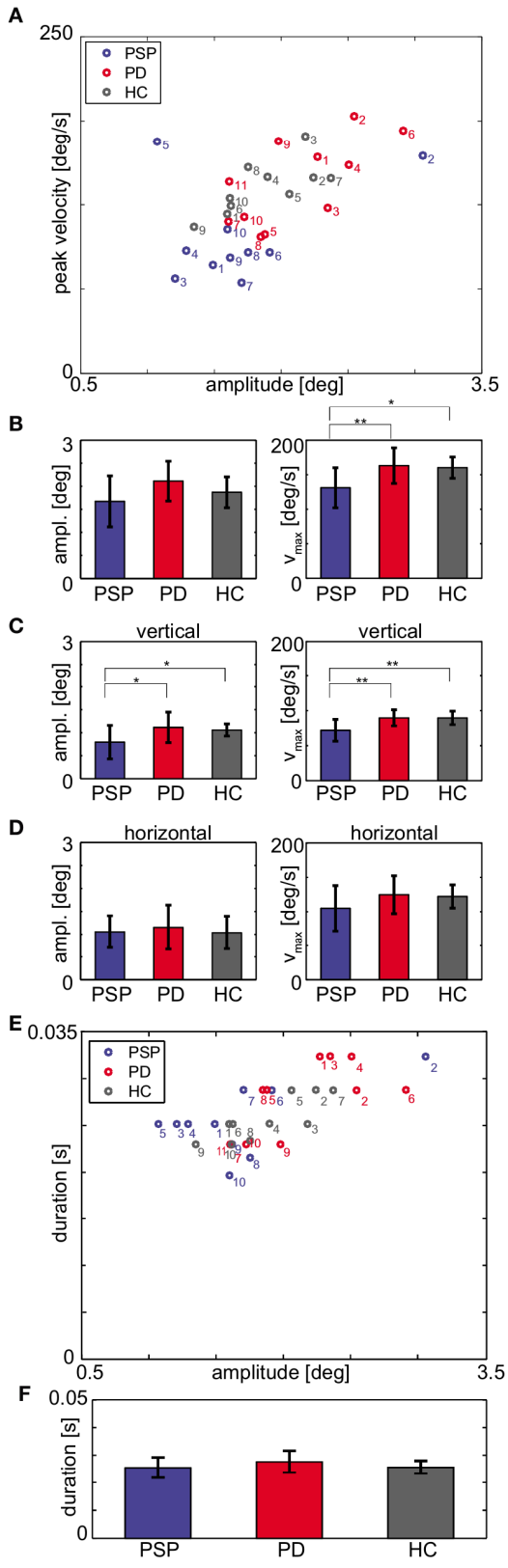

FIGURE 3 | Continued

FIGURE 3 | (A) Medians of saccade peak velocity and amplitude for each participant during real-life measurement. **(B)** Mean over participants of median amplitude (left panel) and median peak velocity (right panel) for each group. **(C)** Vertical component and **(D)** horizontal component of the data of panel **(B)**. **(E)** Medians of saccade duration and amplitude for each participant during real-life measurement; note that the duration is discretized due to sampling frequency **(F)**. Mean over participants of median duration. $^{*}p < 0.05$; $^{**}p < 0.01$.

$[F_{(2,\ 28)} = 1.69, p = 0.20$, **Figure 4B**$]$ and b $[F_{(2,\ 28)} = 1.38, p = 0.27$, **Figure 4C**$]$. There were also no differences between groups in the vertical component of saccades [value of a: $F_{(2,\ 28)} = 2.54, p = 0.097$, **Figure 4D**; value of b: $F_{(2,\ 28)} = 1.08, p = 0.35$, **Figure 4E**] and in the value of the fit parameter a of the functional relationship between duration and amplitude $[F_{(2,\ 28)} = 0.02, p = 0.98$, **Figure 4F**$]$. There was a significant main effect for the values of b in that case $[F_{(2,\ 28)} = 4.11, p = 0.027$, **Figure 4G**$]$ but *post-hoc* t-tests did not reveal significant differences between PSP and PD patients $[t_{(19)} = 1.77, p = 0.09]$ or PD patients and HCs $[t_{(19)} = 1.24, p = 0.23]$. The only significant difference was found between PSP patients and HCs $[t_{(18)} = 2.43, p = 0.026]$.

UNCLASSIFIED EYE MOVEMENTS

Under real-life conditions, fast eye movement phases (saccades), as analyzed above, accounted for only a small amount of the entire measurement time (PSP: $7.6 \pm 3.8\%$, PD: $11.7\% \pm 7.9\%$, HC: $10.4\% \pm 2.8\%$). To compare saccade-based analysis to all eye movements, we generated 2-dimensional velocity histograms for saccades only (**Figure 5A**) and for all eye movements ("unclassified movements," **Figure 5B**) during the entire real-life measuring time. The histograms show pooled data from all participants of each group, normalized such that each participant contributes with equal weight to the respective histograms. In the distribution of saccade peak velocities (**Figure 5A**), a preference for horizontal movements is evident in all groups, which is particularly pronounced in PSP patients, reflecting their prominent reduction in vertical peak velocity. Interestingly, this difference between groups was less evident when analyzing all eye movements (**Figure 5B**). We quantified the spread in each direction by standard deviation. When considering all unclassified eye movements, there were no significant differences among the groups [vertical: $F_{(2,\ 28)} = 1.74$, $p = 0.19$; horizontal: $F_{(2,\ 28)} = 1.86$, $p = 0.18$]. When instead considering saccades only (**Figure 5A**), a picture consistent with the analysis above (section "Real-Life") emerged: the standard deviation of saccade peak velocities yielded highly significant differences between the groups [vertical: $F_{(2,\ 28)} = 8.53, p = 0.001$; horizontal: $F_{(2,\ 28)} = 12.42$, $p < 0.001$]. Significant differences appeared between PSP and PD patients [vertical: $t_{(19)} = 3.38$, $p = 0.003$; horizontal: $t_{(19)} = 4.34, p < 0.001$] as well as between PSP patients and HCs [vertical: $t_{(18)} = 3.41, p = 0.003$; horizontal: $t_{(18)} = 3.75$, $p = 0.002$]. Moreover, when testing analogous measures to those that yielded significant differences and high diagnostic power between patient groups for saccades (**Figures 2** and **3**), no significant effects were found for the full, unclassified eye movement data. For example, the medians of all velocities were not significantly different between the groups

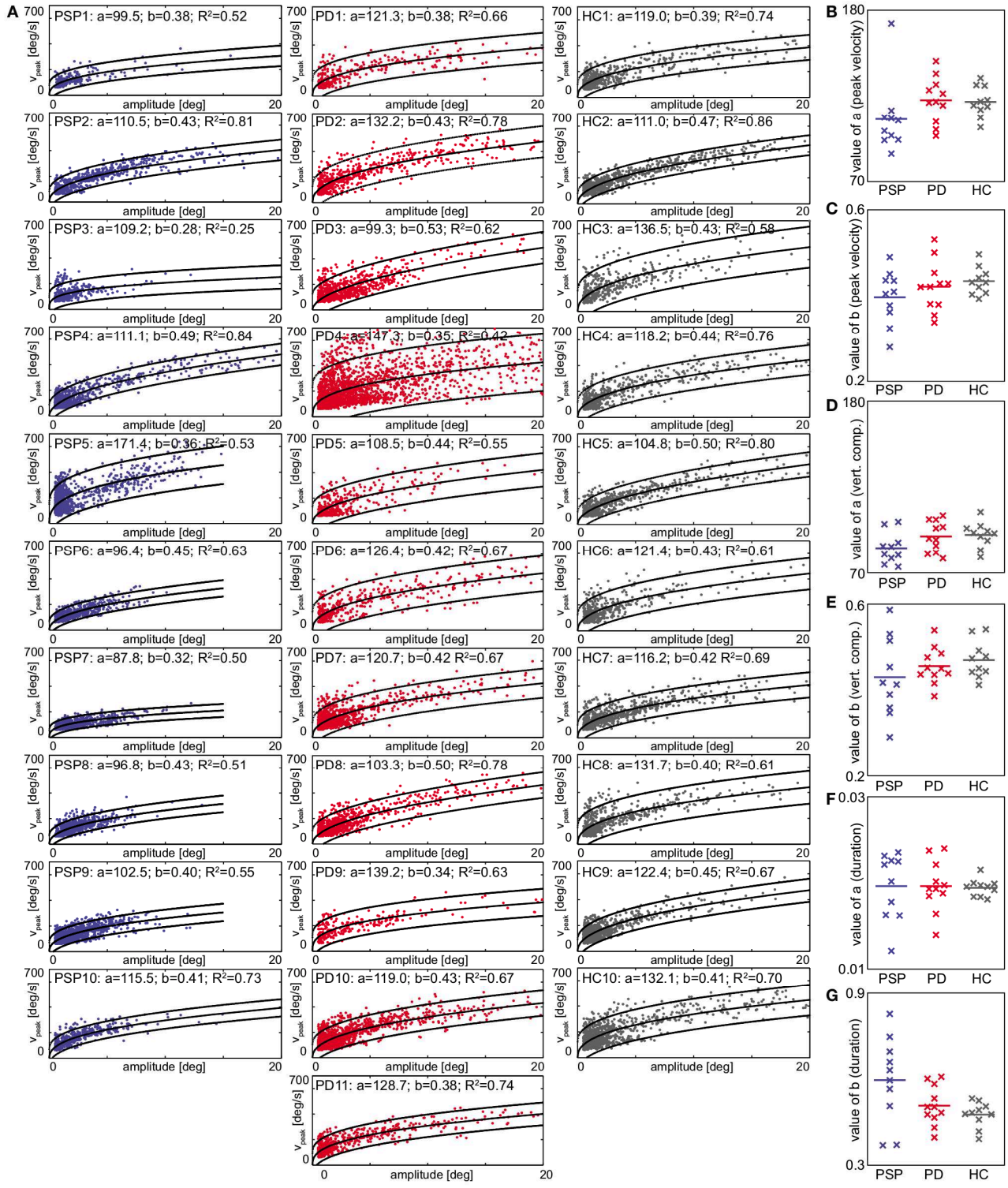

FIGURE 4 | (A) Saccade peak velocity plotted against saccade amplitude ("main sequence") for all individuals. Each data-point corresponds to one saccade (note the cutoff to the bottom and left, given by the thresholds on velocity and duration). Solid black line denotes best fitting power functions (see section "Eye Movements") in a least-squares sense, dotted lines 5 and 95% confidence intervals. Fit parameters and R^2 are given in the panel headers. **(B,C)** Main-sequence fit parameters of the functional relationship between peak velocity and amplitude. **(D,E)** Main-sequence fit parameters for the functional relationship between vertical component of peak velocity and amplitude. **(F,G)** Main-sequence fit parameters for the functional relationship between saccade duration and amplitude.

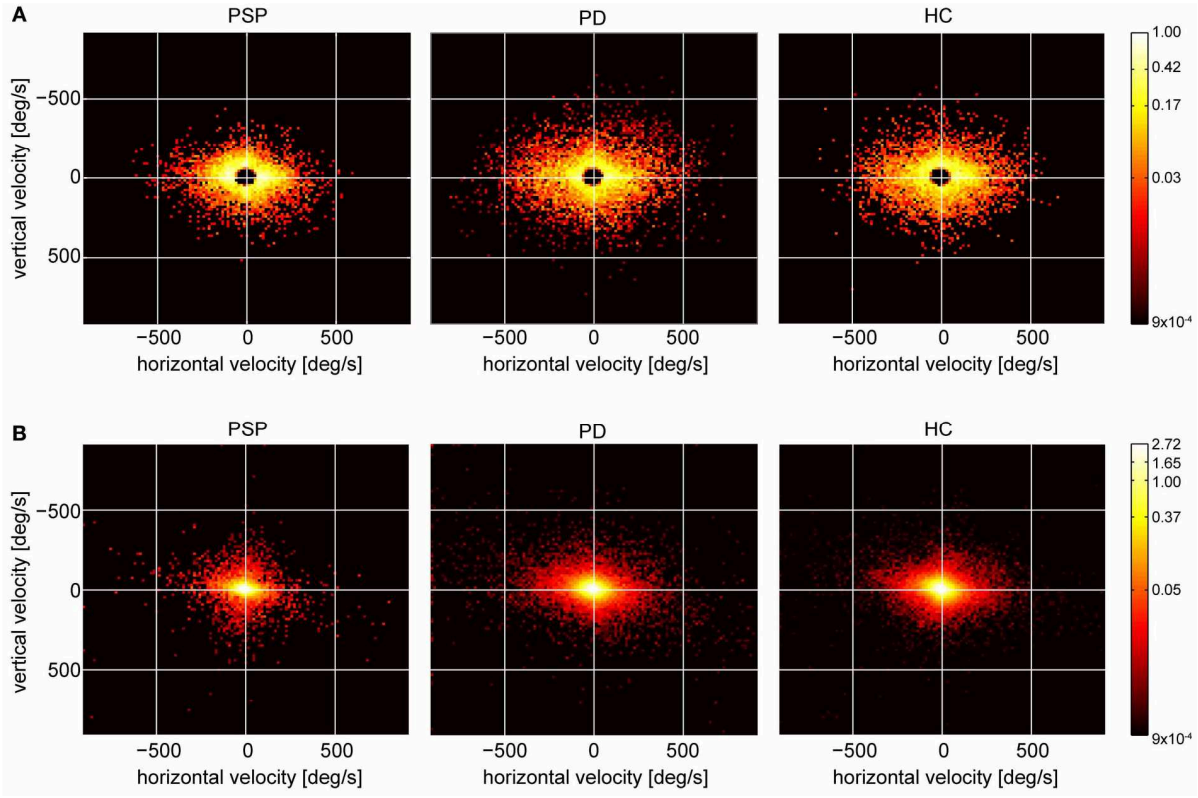

FIGURE 5 | (A) Peak velocity histograms of cumulated saccades of all participants in each group (range: −900 to 900°/s in the cardinal directions, bin size: 15°/s × 15°/s). **(B)** Velocity histograms of raw eye velocities of all cumulated data points of all participants in each group, same range, and bin size as in **(A)**.

$[F_{(2,\ 28)} = 1.01, p = 0.38]$. Notwithstanding some degree of arbitrariness in the definition of saccade thresholds, this indicates that—at least under our recording conditions—the described effects are best observed in fast movements.

HEAD MOVEMENTS

For 26 participants (9 PSP, 7 PD, and 10 HC) we successfully obtained head data during the fixation protocol, for 27 (9 PSP, 9 PD, and 9 HC) during walking along the corridor without target tracking, and for 29 (9 PSP, 10 PD, and 10 HC) while they tracked the stationary target. In the remaining participants, head orientation was not recorded or recording was unsuccessful for technical reasons. We chose to split walking the corridor into periods with tracking and without tracking for head-in-world data considered here, as we expected higher consistency with respect to the overall head movements.

During the fixation protocol, all but one participant deviated less than 2° from their average gaze orientation, 22/26 even less than 1°. Thus, head movements were small and rare, and the median head velocity was below 2°/s in all but one participant. While this implies that participants complied with the instruction to avoid head movements, it also means insufficient movements to obtain robust velocity data.

During tracking, spread (quantified as standard deviations) of head velocities was not significantly different between groups [vertical: $F_{(2,\ 26)} = 0.49, p = 0.62$, **Figure 6A**; horizontal: $F_{(2,\ 26)} = 0.63, p = 0.54$, **Figure 6B**]. During walking without tracking, the vertical spread in velocity showed no dependence on group [$F_{(2,\ 24)} = 0.51, p = 0.61$, **Figure 6C**], either. In contrast, horizontal spread showed a significant group dependence [$F_{(2,\ 24)} = 3.67, p = 0.04$, **Figure 6D**], indicating that the absence of an effect during tracking, where less participants contributed, was not due to a lack of power. Importantly, this group dependence resulted from a difference between PSP patients and HCs [PSP-HC: $t_{(16)} = 3.41, p = 0.004$], but not from a difference between patient groups [PSP-PD: $t_{(16)} = 0.01, p = 0.99$] or between PD patients and HCs [PD-HC: $t_{(16)} = 2.07, p = 0.055$]. In sum, neither head orientation nor head velocity—to the extent they could be analyzed with the present device—could offer any parameters that might serve to discriminate PSP from PD.

DISCUSSION

In the present study we used a novel, wearable eye-tracking device to assess gaze behavior in PD, PSP, and HCs. First, we demonstrate that wearable eye-tracking distinguishes PSP from PD with high sensitivity and specificity. Second, we show that these differences in gaze behavior are most prominent for saccades in a brief fixation protocol and less pronounced in activities of daily living.

The observed differences between saccadic peak velocities in the fixation protocol are highly consistent with earlier findings

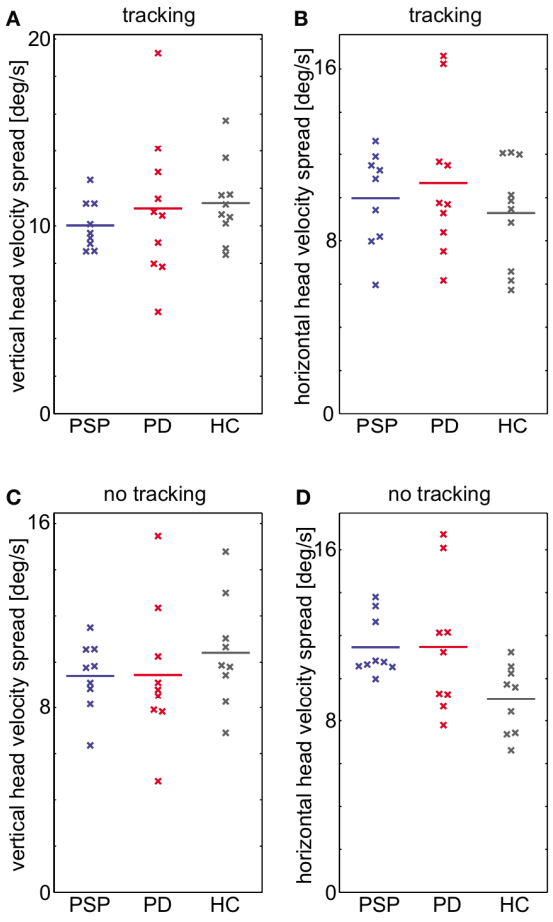

FIGURE 6 | (A,B) Spread of head velocity in **(A)** vertical and **(B)** horizontal direction during walking while tracking a stationary target. **(C,D)** Spread of head velocity in **(C)** vertical and **(D)** horizontal direction during walking without specific instruction. Horizontal displacement of datapoints within groups is for improved visibility only.

(Pinkhardt and Kassubek, 2011; Boxer et al., 2012). Similarly, the lack of evidence for a difference in peak velocities between the PD group and HCs are in line with previous data (Tanyeri et al., 1989; Pinkhardt and Kassubek, 2011). As such, our data extend earlier findings obtained using visually-guided saccades in standard laboratory setups to wearable eye-tracking, which allows efficient assessment of these parameters in less restrained conditions. Even though many sorts of eye movements are affected by PSP, we focused on saccadic peak velocity and amplitude for reasons of efficiency. Duration of saccades as conceivable alternative turned out to have less diagnostic power, despite some difference in the average. Although amplitude, peak velocity, and duration are not independent, but coupled through the "main sequence," the functional fit does not provide any additional diagnostic power in real-life data, and requires more data than available from the 20-s fixation protocol, such that amplitude and peak velocity remain as the main diagnostic markers for this rapid assessment. Still, if these two parameters should turn out to be insufficient for differential diagnosis in a patients with clinically uncertain diagnosis, other eye movements like vergence and the linear vestibuloocular reflex can also be measured with the EyeSeeCam.

The comparison between raw data and data filtered for saccades allows three main conclusions. First, it stresses the specifically prominent impairment of the saccade system for PSP patients as compared to other eye movement systems (Chen et al., 2010). Second, it underlines the importance of objective measurement devices to reliably detect potentially subtle eye movement-related disease markers (Bartl et al., 2009). Finally, the comparably mild differences in overall gaze orienting behavior might point to a strategy how the specific deficits may be compensated for and thus offers a promising path for carefully quantifiable therapeutic intervention (Zampieri and Di Fabio, 2008).

The reduced differences in gaze behavior during activities of daily living indicate that patients at least in part compensate for their ocular motor deficits. Analysis of head movements, however, suggests substantial inter-individual differences, indicating that compensation strategies are largely idiosyncratic. Predicting such compensation behaviors and relating them to other parameters, such as disease progression, will be an interesting issue for further research in larger, heterogeneous PSP cohorts. In a longitudinal study, the precise quantification of compensatory behavior might then also aid the efficient monitoring of treatment success. For differential diagnosis, the free exploration paradigm is clearly less valuable, demonstrating the importance of a flexible, but at the same time standardized fixation protocol for clinical use. Nonetheless, the free exploration data may yield important information on compensation mechanisms and the consequences of the disease on everyday life.

In contrast to eye movements, the parameters considered for head movements did not allow a significant dissociation between patient groups under any of the tested tasks. This could be due to the low spatial and temporal resolution of the head movement measurements as compared to eye movement measurements. It is conceivable that with an improved measurement device for head movements, with different instructions or tasks, or when effects on eye-head coordination are measured with sufficient spatial and temporal accuracy and precision, head movements might eventually become useful and could augment a PSP/PD discrimination system. However, with the present technology and based on the tasks used in the present study, eye velocity and amplitude during the fixation protocol present a most promising candidate for dissociating PSP from PD also in subclinical populations.

This study is to be regarded as a first step toward establishing a new method as a diagnostic tool. Prospective studies measuring eye movements of still unclassified patients are needed to prove that subclinical oculomotor disturbances can be detected prior to the establishment of the clinical diagnosis. Also, square wave jerks which are characteristic of PSP patients could only be detected in one PSP patient, even by careful visual inspection of all eye movement traces. While beyond the scope of the present study, the question as to whether their absence from the measured data is a technical limitation or a true effect of the

population and condition at hand remains an important issue for future research.

Importantly for a possible application in diagnosis and treatment monitoring, the usage of the wearable eye-tracking device is efficient, requiring less than 20-s for the fixation protocol and virtually no device-specific training. While wearable eye-tracking has recently been suggested as tool in a variety of ocular motor and vestibular conditions (Hayhoe and Ballard, 2005; Schumann et al., 2008), the present study demonstrates that wearable eye-tracking also lends itself for efficient clinical use in the context of more complex syndromes, such as typical and atypical Parkinsonism. Whether or not wearable eye-tracking will allow diagnosis beyond the current gold standard obviously can only be established in a long-term longitudinal prospective study, which will apply the criteria found herein already early during disease, when current clinical criteria are not yet clear cut.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http:// www.frontiersin.org/Behavioral_Neuroscience/10.3389/fnbeh.2012.00088/abstract

Movie 1 | Example movies of two participants, PD07 and PSP09, showing a part of the real-life measurement. Histograms picture eye velocity (left panel, range: −500 to 500°/s in the cardinal directions, bin size for this movie: 5°/s × 5°/s) and head velocity (right panel, range: −60 to 60°/s in the cardinal directions, bin size: 3°/s × 3°/s).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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3. General discussion and outlook

In this thesis I used psychophysical, electrophysiological and neuropsychological methods to investigate the effect of a stable and complete perceptual representation of our world despite the various challenges the visual system has to cope with caused by eye-movements and self-motion. In addition, I was interested in the transferability of well established results of eye-movement studies from laboratory measurements to the real world. My work aimed to utilize eye-tracking to shed light onto the underlying neuronal mechanisms ensuring perceptual stability and, more specifically, causing eye-movement dysfunctions in neurological or psychological patient groups and even during healthy aging.

3.1. Perceptual stability and visual mislocalization

One possibility of the visual system to achieve perceptual stability is to encode visual input in a world-centered frame of reference. For this purpose in a first step the originally retinocentric input has to be transformed into a craniocenric frame of reference (Zipser & Andersen, 1988; Snyder et al., 1998; Salinas & Abbott, 2003). This transformation of coordinates could be realized by a combination of information on the retinal location of a stimulus and information about an ongoing eye-movement and/or the current eye position, respectively (Hazelhoff & Wiersma, 1924; Bremmer et al., 1998; Boussaoud & Bremmer, 1999). These latter, so called efference copy (von Holst & Mittelstaedt, 1950) or corollary discharge signals (Sperry, 1950) are thought to represent an internal copy of the motor plan associated to each movement to help with the attribution of agency and even predict the outcome of certain actions (Blakemore et al., 2000). These signals represent the perfect candidate to inform the visual system about an upcoming shift of the visual field due to an eye movement and simultaneously provide the necessary information to properly account for them.

The first study of my thesis investigated the mechanism of a combination of the retinal stimulus location and an internal eye-position signal during different kinds of eye-movements as a source to generate perceptual localization of stimuli in the world. Here stimuli were monocularly presented close to blind spot, an area where no photo receptors are available to physically detect the stimuli. Yet, subjects localized stimuli within that area

they should be blind for. The amount of localizations and the side of the blind spot in which perceptual localization was shifted into was directly related to the mislocalization of the corresponding eye movement for each subject. Furthermore, the area with the least perceived localizations, which is related to the physiological blind spot but applied for perceived positions, shifted along with the specific mislocalization induced by each eye movement and subject while preserving its general shape. This suggests that the entire visual map signal of actual retinal target locations, including the blind spot, is combined linearly with an independent signal carrying information about the ongoing eye movement to form a perceptual map of target locations. As this combination induces a perceptual shift of stimulus positions into regions the subjects should be blind for, a probable candidate for this signal is the efference copy of eye-position. The hypothesis of an initially correct spatial representation, which later gets combined with an eye-position signal, is in line with a neurophysiological study showing that the location of visual receptive fields in area MT of the macaque are, at least at that processing stage, not modulated by slow eye-movements (Hartmann et al., 2011). Altogether, this predicts the neuronal basis of localization in a rather high area of the dorsal stream. A possible candidate for this area should map a complete representation of the visual environment and has to have an internal representation of eye-position readily available. Area VIP for which a functional equivalent has been identified in humans (Bremmer et al., 2001) is a possible candidate of such an area. Recent studies have shown that area VIP holds neurons that encode information in different frames of reference from eye-centered, over intermediate to head-centered (Schlack et al., 2005), suggesting that there are coordinate transformations happening in that area. This latter suggestion is based on the finding that response latencies of visual cells were shorter for those cells encoding visual information in eye-centered coordinates than in this cells encoding visual information in head-centered coordinates. Cells encoding in an intermediate reference frame had medium latencies.

Additionally area VIP is a polymodal area in which information from various senses, i.e. vision, sense of balance, somatosensation and audition converge (Avillac et al., 2005, 2007; Bremmer et al., 2002a, 2002b; Chen et al., 2011; Duhamel et al., 1998; Schlack et al., 2002). Hence, with this rich source of multimodal information even higher order coordinate transformations to a body- or even world-centered frame of reference might be possible

within this area, which would eventually provide a mechanism to facilitate perceptual stability.

In the second study of my thesis I aimed to find the neuronal correlate of the perceptual mislocalization during eye movements utilized in study one. A recent study of Morris and colleagues (2012) suggested an erroneous internal eye-position signal as the source of the perceptual mislocalization of briefly flashed stimuli during saccadic eye-movements. Here I tested if this hypothesis can be extended to smooth eye-movements and if internal eye-position signals in the brain are sufficient to accurately represent the actual eye-position over the course of a smooth pursuit eye-movement. Indeed, there are many areas in the primate brain in which neurons modulate their firing rate with changes of the current gaze direction, i.e. in striate (Trotter and Celebrini, 1999), extrastriate (Galletti & Battaglini, 1989; Bremmer et al. 1997a; Bremmer, 2000), parietal (Andersen & Mountcastle, 1983; Bremmer et al., 1997b, 1999; Morris et al., 2012, 2013) and even premotor cortex (Boussaoud et al., 1998). This relationship between the neuronal discharges and the current eye position forming an “eye-position field” is thought to reflect an efference copy signal. Recent studies showed that these eye-position signals in four parietal areas (i.e. area MT, MST, LIP, VIP) are highly accurate and sufficiently fast to be reliably used for a transformation of reference frames during steady fixation and saccade eye-movements (Morris et al., 2012, 2013). The second study in this thesis confirmed the results of Morris and colleagues and showed that area VIP also provides an efference copy signal of eye-position of considerable accuracy during smooth pursuit eye-movements. At the same time, the temporal and spatial mismatches between the decoded eye-position and the actual eye-position offer a potential explanation for the psychophysically observed mislocalization effects of briefly flashed stimuli during different kinds of eye movements. Indeed, an erroneous internal eye-position signal with comparably slow dynamics, which predictively shifted already prior (<100 ms) to a saccade but caught up to the actual eye-position only shortly (~200 ms) after the eye had moved, was identified as a potential neuronal correlate of perisaccadic mislocalization of briefly presented stimuli (Morris et al., 2012). Likewise, study two in this thesis showed an inaccuracy of the efference copy signal, i.e. a constant lead of the decoded eye-position of about 1.4° as compared to the actual eye-position during steady state pursuit. This lead offers an explanation for the observed mislocalization during the slow phase of look-OKN, which has a similar magnitude (Kaminiarz et al., 2007) and has been identified to share a lot

of common features with SPEM due to activation in similar motion sensitive and eye-movement areas in the brain (Konen et al., 2005). Furthermore, the combination of a constant lead of the decoded eye-position with a biased allocation of attention in front of the pursuit target as demonstrated by Kahn and colleagues (2010) can be transformed into a spatial (mis-)localization map. Remarkably, the resulting 2-D error pattern nicely fits the behaviorally measured asymmetric mislocalization pattern during smooth pursuit eye-movements (Figure 5).

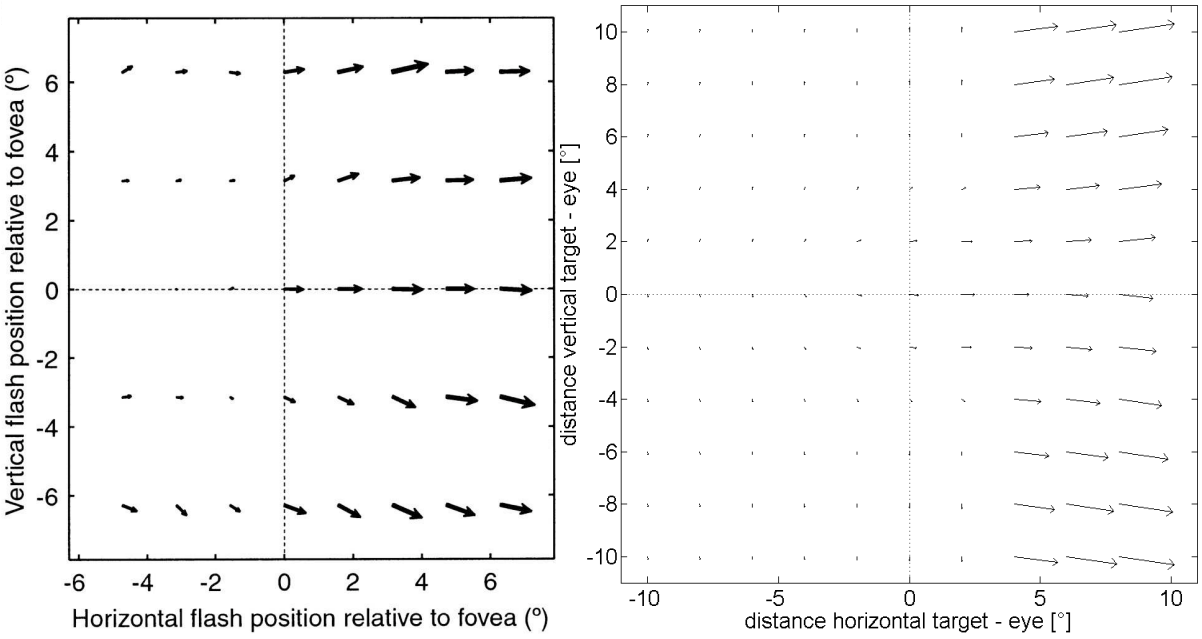

Figure 5: *Comparison of psychophysically measured mislocalization during rightward smooth pursuit (A) and modeled mislocalization caused by a constant lead of decoded eye-position and an attentional distortion of the perceptual space (B). Both figures show the same asymmetric pattern with a considerable mislocalization in direction of the ongoing pursuit, but almost no mislocalization in the visual hemi-field behind the eye. A: after van Beers et al., (2001).*

Taken together, the first two studies of this thesis support the hypothesis that the motion selective areas in the parietal cortex and specifically area VIP offers the relevant neural signals to perform a coordinate transformation of visual signals from the permanently varying retinal input to a non-retinal reference frame enabling a consistent and stable perception of our environment. Furthermore, perceptual mislocalization occurring when the visual system is psychophysically pushed to its limits might represent a potential drawback of the cognitive mechanism ensuring perceptual stability, which possibly results from a

trade-off between a spatially accurate efference copy signal and the dynamic and predictive capabilities of the visual system.

Another mechanism suggested to be related to perceptual stability is predictive remapping. It was described first for neurons in area LIP (Duhamel et al., 1992) and since then was replicated in other visual and visuo-motor areas like the frontal eye-fields (Umeno & Goldberg, 1997; Nakamura & Colby, 2002). Neurons typically are characterized by their receptive field (RF), an area in which stimulation modulates the neuron's activity. During predictive remapping a neuron changes its discharge prior to the initiation of a saccade, as if it already responds to stimuli at its future receptive field, after the eye would have moved. Thus, this mechanism anticipates upcoming changes of the spatial representation associated with an eye movement and is able to account for them, thereby maintaining perceptual stability within an eye-centered frame of reference. Yet, until now the mechanism of predictive remapping has been shown only to achieve trans-saccadic stability, whereas verification of an influence to perceptual stability in general is still missing.

The specific contribution from the representation of spatial information in non-retinotopic reference frames, as well as predictive remapping of retinocentric information to perceptual stability across eye movements and self-motion is still under investigation. This thesis aimed to complement the current knowledge and provided a potential context and source to perceptual mislocalization effects during eye movements.

3.2. Differences, challenges and advantages of eye-movement studies in the real world

When stepping outside the controlled environment of the laboratory, the visual system and perceptual stability gets particularly challenged not only by various eye movements, but also by head-, body- and self-motion (Bremmer & Krekelberg, 2003). Primates have evolved to deal with these challenges appropriately. Yet, it is not self-evident, that results from laboratory studies can be transferred to the real world without further verification. On the other hand, eye-movement studies in the real world offer the possibility to explore the visual system in total and to examine different groups of patients due to the mobility and simplicity of modern mobile eye trackers, which otherwise would not be feasible.

Study one and two of my thesis showed, that the availability of an efference copy signal of eye-position in the brain is essential for the visual system to perform optimally and to achieve perceptual stability including characteristic perceptual localization errors. Patients with schizophrenia are thought to have a misattribution of agency of their own thoughts and actions (Frith, 1992), which is thought to be due to a dysfunctional efference copy mechanism (Feinberg, 1978, Kircher & Leube, 2003; Leube et al., 2010). Therefore, schizophrenia patients offer a great possibility to investigate the consequences of an impaired efference copy mechanism to eye movements and perception. There is already some evidence from psychophysical studies of an overall failure in using extraretinal motion information derived from an efference copy signal in schizophrenia patients (Spering et al., 2013). As suggested by the importance of the efference copy signal to visual perception in the first two studies in this thesis, a visual localization task would be a particularly interesting study to perform in the future with schizophrenia patients, which to the best of my knowledge has not been done so far. Besides that, a study of Lindner and colleagues (2005) found that self-induced information, i.e. retinal image motion resulting from smooth pursuit eye-movements, during a motion-perception task is misattributed to the background motion in schizophrenia patients suffering from delusions of influence. Similarly, visual motion information from the environment during self-motion could be misattributed in these patients. Such misattribution of sensory consequences challenges the stable perception of the world. Hence, the third study in this thesis investigated the eye-movement behavior of schizophrenia patients and healthy controls in a real world environment, to verify the numerous eye-movement abnormalities of schizophrenia patients found in the laboratory and to explore their perception in a more natural setting. Diefendorf & Dodge (1908) were the first, who quantitatively analyzed the eye-movements of schizophrenia patients and who found an impairment of smooth pursuit eye-movements with a decreased gain, which has been frequently reproduced ever since (Holzman et al., 1974; O'Driscoll & Callahan, 2008). Smooth pursuit relies on visual motion information on the retina ('retinal slip') (Ilg, 1997) as well as an efference copy signal consisting of extraretinal information about the ongoing eye movement and eye position (Thier & Ilg, 2005). A failure in integrating these extra retinal signals, could account for the dysfunction of smooth pursuit eye-movements in schizophrenia patients. Yet, during everyday life humans usually don't perform pure SPEM of a well isolated target, but rather actively track certain aspects within a moving visual field or

passively view the motion of the entire visual field (Niemann et al., 1999). This active tracking resembles smooth pursuit eye-movements by serving the same purpose, i.e. stabilizing an object on the fovea which moves through the visual field, with the exception that the later is performed with no additional self-motion. In the third study of this thesis I showed that specific eye-movement dysfunctions in schizophrenia occurred in laboratory measurements and the real world, while others seemed to disappear in a more natural context. The visual tracking of a fixed object on the ground during self-motion, although closely related to smooth pursuit, did not show a reduced gain typically observed in schizophrenia patients. We hypothesized, that this difference was due to the environment offering patients a variety of compensatory mechanisms (e.g. head movements, information about optic flow, other objects as visual landmarks, etc.) to equalize their specific deficits like an impaired efference copy signal or a misattribution of sources of information to eventually overcome at least some of their visual impairments. The relevance of a variety of different sensory cues to the visual system of schizophrenia patients in order to perform well was shown by Holzman (2000). When additional non-velocity cues (e.g. position changes or contrast diminution) were artificially removed from a stimulus the performance to discriminate certain stimulus velocities got significantly worse in schizophrenia patients. Yet, such cues are almost always available in the real world and can be used to perhaps support or even substitute certain aspects of vision in order to preserve visual perception as effectively as possible. On the other hand, it seems that certain aspects of vision and eye movements are generally affected in schizophrenia patients, e.g. they perform less exploratory eye-movements, which was also shown in the laboratory (Kojima et al., 2001; Egaña et al., 2013). At the same time, other abnormalities might get compensated by alternative mechanisms under certain behavioral or environmental conditions, to keep visual perception generally intact. Taken together, a large number of open questions remain that underline the need to perform research in the real-world and complement laboratory studies, to better understand the neural basis of visual perception and the control of eye-movements in the healthy and diseased brain.

This conclusion is in line with the results of the forth study of this thesis showing that eye-movement abnormalities previously described in the laboratory, not only in certain brain diseases but also during healthy aging, can not be transferred one-to-one to the real world. In this study I could show that oculomotor performance as measured by basic eye-

movement parameters like saccade amplitude and peak-velocity significantly decreases with increasing age, typically starting already around the age of 25 (Morgan, 1993; Munoz et al., 1998). While this study confirmed some of the previous results from laboratory measurements (Sharpe & Zackon, 1987; Irving et al., 2006) or even clarified inconclusive results on saccade peak-velocity (Henriksson et al., 1980; Munoz et al., 1998), other findings in our study comparing the natural tracking of an object during self-motion with smooth pursuit eye-movements as measured in the laboratory (Moschner & Baloh, 1994; Ross et al., 1999) did not show the general deterioration of tracking gain associated with senescence.

The forth study revealed an additional difference between measurements in the real world and in the laboratory. While the latter usually examines discrete domains of eye-movement characteristics, e.g. saccades of a certain amplitude (e.g. Munoz et al., 1998 investigated only saccade with an amplitude of 20°) or smooth pursuit with a particular velocity (e.g. just one velocity of 16.7°/s in Ross et al., 1999), eye-movement parameters in the real world are usually continuous and non-normally distributed (Land et al., 1999, Pelz & Rothkopf 2007). Especially saccades with small amplitudes of less than 5° are usually omitted in laboratory experiments, although those represent the majority in everyday vision as shown by Land and colleagues (1999) and study three and four in this thesis. As a consequence, some results collected under laboratory conditions could be biased and thus might miss or misestimate some effects of oculomotor functioning. Indeed, in study three saccade peak-velocities in schizophrenia patients only showed significant differences compared to healthy controls for saccade amplitudes of less than three degree. When analyzing the entire range of amplitudes no effect was noticeable. Then again, in study four of this thesis the saccade peak-velocity was significantly lower for the elderly for all separately analyzed amplitude ranges as well as for the total range. This finding emphasizes the need to carefully choose the parameters of an experiment, which is meant to investigate normal vision.

Overall, the examination of eye-movements in the real world during self-motion introduces a much higher relevance of the parietal areas of the brain in contrast to laboratory measurements. This allows investigating their actual impact on and interaction with eye-movements during navigation trough space in its full context. Especially the motion sensitive areas MST and VIP are crucial for the evaluation of self-motion information like the direction of heading and the integration of optic flow information. Despite several eye-movement impairments in the elderly as shown by study four, heading detection via expanding artificial

radial flow fields relative to a reference has been shown to be unaffected by age (Billino et al., 2008). On the other hand, a recent study using a virtual-reality setup with 3-D clouds of dots showed a decreased absolute heading performance of older participants (Lich & Bremmer, 2014). The authors explained these results with an anatomically suggested age dependent loss of neurons of 1-2% per decade (Jäncke, 2004; Raz et al., 2005) and verified their hypothesis by introducing such a cell loss into a neuronal network previously used to describe the behavior of areas MT and MST for heading detection (Lappe & Rauschecker, 1993; Lappe et al., 1996). This explanation of a neuronal cell loss could also be applied to the impaired eye-movement parameters in the elderly found in study four. Indeed, a study of Lee et al. (1988) found that inactivation of a subpopulation of neurons in the superior colliculus, significantly decreased saccade velocity and suggested that eye-movement parameters like direction, amplitude and velocity are based on the response of the entire population of neurons. In contrast to the theory that information is extracted only from the most active cells of a population, this population-averaging hypothesis is in agreement with the results of the second study in this thesis, showing that the population of VIP neurons contains an almost accurate eye-position signal, which deteriorates with a decreasing number of neurons contributing to the decoding (Figure 6). A similar relation has been shown for population coding of other parietal areas (Bremmer et al., 1998; Morris et al., 2013) as well as premotor areas (Boussaoud & Bremmer, 1999) and visual cortex (Vogels 1990).

Although the studies of Billino et al. (2008) and Lich & Bremmer (2014) suggested, that parietal areas are affected by aging, the results of study four in this thesis imply that self-motion information is adequately integrated with eye movements in the elderly. This integration is crucial for the execution of compensatory eye-movements to counterbalance the motion of the target in the visual field due to the self-motion in order to ensure the visual tracking of an object during self-motion with a high gain as shown in the elderly in study four. Likewise and in contrast to efference copy signals of ongoing eye-movements, self-motion information seems to be unimpaired and readily available in schizophrenia patients, as shown by their normal tracking performance of a fixed object during self-motion in study three of this thesis.

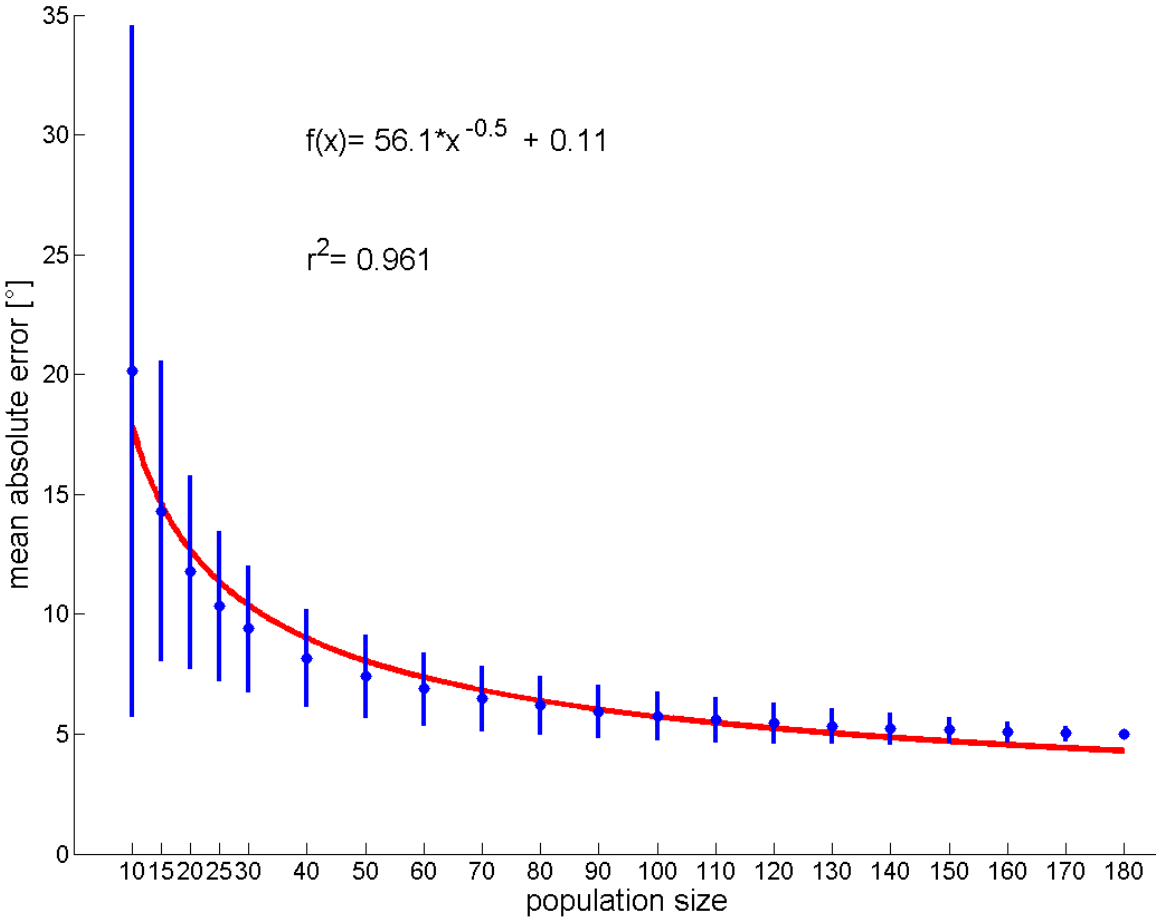

Figure 6: Mean error of the predicted eye-position as compared to the real eye-position during smooth pursuit as a function of population size of neurons in area VIP.
Mean errors (blue dots) and standard deviations (blue lines) were computed by randomly selecting 100000 subsets of neurons from each given sample size (n = 10, 15, 20, 25, 30, 40, …). This led to a monotonically decreasing error with an increasing number of neurons, which could be fitted by an inverse square root function. This functional approach suggests a highly accurate and reliable representation of eye-position information in the whole population of neurons in area VIP, e.g. roughly 4000 neurons are needed for an internal eye-position representation during SPEM with a mean deviation of less than 1°.

Especially the multimodal area VIP might play an exceptional role during real-world behavior, which could have been underestimated in previous laboratory studies. This thesis in addition to previous neurophysiological work (Avillac et al., 2005, 2007; Bremmer et al., 2002a, 2002b; Chen et al., 2011; Duhamel et al., 1998; Schlack et al., 2002) identified this area as a vital hub for combining information from different sensory modalities. Thus the broad spectrum of signals available in this area might offer a variety of possible ways to compensate for dysfunctions of a few other information sources and provides crucial data

for the execution of coordinate transformations of sensory signals, eventually supporting a stable perception of our world.

The investigation of effects of healthy aging on basic eye-movement parameters is getting more and more important in our senescent society in order to identify the underlying changes in the brain during the process of aging. Since the probability of an onset of many diseases increases as we are getting older, it is particular important to identify the common influences of healthy aging on eye movements and the brain in general in order to not falsely attribute them to a possible disease. If we are able to clearly identify eye-movement abnormalities associated with healthy aging, we can precisely associate additional eye-movement characteristics to certain diseases. This approach would allow us to reliably use eye movements und their deviations to examine brain diseases in order to gain deeper insights into the mechanisms and the underlying causes of brain disorders (cf. 1.4.1) and eventually identify objective and quantifiable parameters to support the diagnosis. As a first step, study five of this thesis investigated eye movements and their potential use for the diagnosis and differentiation of patients with idiopathic Parkinson's disease (IPD) and a related atypical form of Parkinson's disease called progressive supranuclear palsy (PSP). These diseases have similar onsets challenging an early differential diagnosis. Unfortunately, both diseases show a rather different progress and prognosis, requiring different types of treatments (Burn & Lees, 2002). Therefore it is vital to differentiate these two diseases from each other as early as possible, to ensure an optimal therapy. We utilized the advantages of a mobile eye-tracker like transportability and the simplicity of setup to bring the laboratory to the patient, which is of particular importance in these patient groups due to their often impaired physical constitution. We could show that basic eye-movement parameters like saccade velocity and amplitude in a simple sequence of gaze shifts were able to reliably differentiate PSP patients from PD patients and healthy controls with specificities and sensitivities of up to 100% for certain parameters like saccade peak-velocity in the vertical direction. Likewise other studies of eye-movements in schizophrenia have shown the capability to differentiate patients from healthy controls with a sensitivity of 89.0% and a specificity of 86.7% using exploratory eye-movements of an artificial figure (Kojima et al., 2001).

Just as study three and four in this thesis, the last study revealed some aspects of the eye-movement system to be specifically affected, i.e. the saccadic system, while others proved to

work relatively normal or were only mildly affected in the patient group, e.g overall exploratory gaze behavior. Although the results of the saccade parameters in study five are conclusive, this study shows that it is not always necessary or sometimes even deconstructive to investigate unrestricted natural eye-movement behavior. In this study the most obvious differences between PSP patients and PD patients could be found in a standardized fixation protocol in which predefined targets were projected on a wall and subsequently fixated without any other head- or body movement. Such a paradigm closely resembles a typical measurement in the laboratory and deliberately renounces other mechanisms, which might influence or even compensate the eye-movement dysfunction under consideration. Yet, mobile eye-trackers provide the most convenient way to measure the eye movements of patients directly in the clinic as a complement to common screenings within a whole battery of tests or even at the bedside of completely immobile patients (Stoll et al., 2013). Overall, the capabilities and versatility of eye-movements and especially the application of mobile eye-trackers as an objective and efficient tool supporting the (differential-)diagnosis and observation of specific diseases are largely unused in the daily clinical routine. Future studies have to prove the usability of eye tracking in detecting even subclinical oculomotor dysfunctions reliably in a wide range of neurological and psychiatric diseases and should be able to attribute them to a specific disease with certainty in order to outperform currently used techniques.

Taken together, study three to five nicely show the various advantages but at the same time challenges of eye-movement studies in the real world and emphasize the importance of a correct interaction of all methodological variables like the used paradigm and the eye-movement parameter under investigation. One the one hand, real life eye-movement studies are capable to reveal a deeper insight and provide a more complete understanding of the visual system (preserved tracking gain in schizophrenia patients and the elderly in study three and four). Finally, commonly known laboratory results sometimes basically resemble those measured in the real world (saccade dynamics during aging and in PSP patients in study four and five). Then again, the controlled conditions in laboratory tasks appear to be better suited to detect eye-movement impairments reliably (diagnostic capability of saccade parameters for PSP patients in study five). Unfortunately, there is not a single best method to investigate eye movements. It is inevitable to consider all techniques

used to examine eye movements and their capabilities to choose the right method in order to study a research question optimally.

In conclusion, my thesis emphasizes the importance of a combination of psychophysical studies in the laboratory for the general examination of a well defined aspect of the eye-movement system or perception and neurophysiological studies in the animal model to identify their underlying neuronal mechanisms. Furthermore, real-world studies on healthy humans are needed to transfer findings onto the human framework as well as neuropsychological studies to find clinical applications and eventually improve the diagnosis, treatment or outcome of brain diseases. Only this comprehensive combination allows us to obtain a more complete picture and understand perception within a broader perspective. This holistic approach became feasible in recent years by the constant progression of techniques (e.g. mobile eye-tracking, single cell recordings in the head-free monkey (e.g. Keith et al., 2009; Sajad et al., 2014) or the freely moving mouse (e.g. Lin et al., 2006; Kralj et al., 2012)) and inspires completely new interdisciplinary research allowing to better understand how the brain works.

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Declaration of the authors' contributions to the studies

This thesis consists of 5 studies I co-authored, which are partly published in peer-reviewed journals or are currently prepared for publication.

Chapter 2.3.:

Stefan Dowiasch, Janne van Aswegen & Frank Bremmer (in preparation).
Monocular visual localization during eye movements

The study was planed by **SD** and FB in the scope of a work group internship of **SD**. **SD**, bachelor student JA under supervision of **SD** & student research assistant MK conducted the experiment after instruction and training by **SD**. The analyses of the experiments were done by **SD** and JA. Part of the data was included in the bachelor thesis of JA conducted under the supervision of **SD**. All data were reanalyzed by **SD**. The chapter was written by **SD**.

Chapter 2.4.:

Stefan Dowiasch, Gunnar Blohm & Frank Bremmer (in preparation).
Neural basis of spatial mislocalization during smooth eye-movements

The study reanalyzed previously published data collected by AS. The novel approach was planed by **SD** and FB. Data was reanalyzed by **SD**. GB provided significant input to the model. The chapter was written by **SD**.

Chapter 2.5.:

Stefan Dowiasch, Bianca Backasch, Wolfgang Einhäuser, Dirk Leube, Tilo Kircher & Frank Bremmer (2014). Eye movements of patients with schizophrenia in a natural environment

This study was planned in the scope of a diploma thesis (Dowiasch, 2010) by **SD**, WE, TK and FB. BB and DL gave access to the patients. Part of the data was included in the diploma thesis of **SD**. Substantially more data were recorded during the PhD time of **SD** by **SD**, BB and DL. **SD** reanalyzed all data and wrote the mansucript. All authors proofread the manuscript.

Chapter 2.6.:

Stefan Dowiasch, Svenja Marx, Wolfgang Einhäuser & Frank Bremmer (2015).
Effects of Aging on eye movements in the real world

The study was planed by **SD**, SM, WE and FB. The data were recorded by **SD** and SM and analyzed by **SD**. The manuscript was prepared by **SD**. SM, WE & FB supervised data analysis and proofread the manuscript.

Chapter 2.7.:

Svenja Marx, Gesine Respondek, Maria Stamelou, **Stefan Dowiasch**, Josef Stoll, Frank Bremmer, Wolfgang Oertel, Günther Hoglinger & Wolfgang Einhauser (2012).
Validation of mobile eye-tracking as novel and efficient means for differentiating progressive supranuclear palsy from Parkinson's disease

Authors' contribution: SM, MS, FB, WHO, GUH and WE conceived the study; GR, MS, WHO and GUH gave access to patients; SM, GR, MS and **SD** collected the data; JS provided technical support; SM, **SD** and JS analyzed the data; GR,SM and WE wrote the article, all authors proof-read the article.

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