Review

Smooth pursuit eye movements and schizophrenia: Literature review

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Abstract

Objective: To review the scientific literature about the relationship between impairment on smooth pursuit eye movements and schizophrenia.

Methods: Narrative review that includes historical articles, reports about basic and clinical investigation, systematic reviews, and meta-analysis on the topic.

Results: Up to 80% of schizophrenic patients have impairment of smooth pursuit eye movements. Despite the diversity of test protocols, 65% of patients and controls are correctly classified by their overall performance during this pursuit. The smooth pursuit eye movements depend on the ability to anticipate the target’s velocity and the visual feedback, as well as on learning and attention. The neuroanatomy implicated in smooth pursuit overlaps to some extent with certain frontal cortex zones associated with some clinical and neuropsychological characteristics of the schizophrenia, therefore some specific components of smooth pursuit anomalies could serve as biomarkers of the disease. Due to their sedative effect, antipsychotics have a deleterious effect on smooth pursuit eye movements, thus these movements cannot be used to evaluate the efficacy of the currently available treatments.

Conclusion: Standardized evaluation of smooth pursuit eye movements on schizophrenia will allow to use specific aspects of that pursuit as biomarkers for the study of its genetics, psychopathology, or neuropsychology.

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Movimientos de seguimiento ocular lento y esquizofrenia: revisión de la literatura

RESUMEN

Objetivo: Revisar la literatura científica sobre la relación entre las alteraciones en los movimientos oculares de seguimiento lento y la esquizofrenia.

Métodos: Revisión narrativa de la literatura que incluye artículos históricos, reportes sobre investigación básica y clínica, revisiones sistemáticas y meta-análisis sobre el tema.

Resultados: Hasta el 80% de los pacientes con esquizofrenia tienen alteraciones en los movimientos de seguimiento ocular lento. A pesar de la diversidad de protocolos de evaluación, el 65% de los pacientes y de los controles son clasificados correctamente por su rendimiento global durante dicho seguimiento. Los movimientos de seguimiento ocular lento dependen de la capacidad de anticipar la velocidad del blanco y de la retroalimentación visual, así como del aprendizaje y la atención. La neuroanatomía implicada en el seguimiento lento se superpone en alguna medida con la de ciertas zonas de la corteza frontal relacionadas con algunas características clínicas y neuropsicológicas de la esquizofrenia, de modo que algunos aspectos específicos de la alteración en el seguimiento lento podrían servir como biomarcadores de la enfermedad. Como consecuencia de su acción sedante, los antipsicóticos tienen un efecto deletéreo sobre los movimientos de seguimiento ocular lento, por lo que dichos movimientos no pueden usarse para valorar la eficacia de los fármacos disponibles en la actualidad.

Conclusión: La evaluación estandarizada de los movimientos de seguimiento ocular lento en la esquizofrenia permitirá utilizar aspectos específicos de dicho seguimiento como biomarcadores para el estudio de su genética, psicopatología o neuropsicología.

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Introduction

Schizophrenia is a chronic disease that affects nearly 1% of the population and has a negative impact on individual performance at the personal, social and labor level. In this disease, thought content and forms are altered as well as perception, psychomotricity and emotional expression. Alterations in smooth pursuit eye movements have been represented in several studies on schizophrenia more than other variables such as minor physical anomalies or reduced gray matter. Up to 80% of patients with the disease and 50% of their first-degree relatives exhibited difficulties in smooth pursuit eye movements.

In order to explain said movements, let us imagine a situation in which an individual is watching a bird in flight, which induces ocular movements to follow the movement and keep it in focus. The function of slow pursuit movements is to maintain the retinal image of a moving object within the fovea, in contrast with saccadic (brief and fast) movements which have the aim of redirecting the gaze. Both types of movements can supplement each other, as saccadic movements have the ability to correct deviations during slow pursuit.

Neuro-ophthalmological research in psychiatry is over one century old. In 1908, Diefendorf and Dodge published their pioneering study on “ocular reactions” in psychiatric patients by means of “photochronographs” which used photographic recordings. The group led by Holzman (1973) was the first to study smooth pursuit movements using electro-oculogram (EOG) in patients with schizophrenia. Knowledge about the physiology of ocular movement, obtained by means of studying primates (including humans with brain injuries), can shed light on the physiopathology of mental disorders. In addition, alterations in smooth pursuit movement could serve as biomarkers in schizophrenia.

A biomarker is an objective indicator of the particular condition of an organism, i.e., a verifiable characteristic in the presence of a specific disease which otherwise would be absent. Biological markers are useful because on the one hand they can be the basis for clinical tests to divide the population between healthy and unhealthy individuals, while on the other hand they could provide information about the severity and evolution of patients.

The present article is a review of scientific literature on the relationship between smooth pursuit eye movement alterations and schizophrenia.

Functional neuroanatomy and cognitive processes of smooth pursuit movements

Smooth pursuit movements involve transformation mechanisms at the sensory-motor and cognitive level. Pursuit is maintained due to 2 factors, i.e., prediction (anticipation) of the speed of the target and visual feedback on performance. The combination of these 2 elements of information (retinal and extra-retinal) involves the entirety of various channels.

During the first 50–100 ms (initiation or open phase), ocular pursuit is directed by information on the movement received through the eyes and therefore involves the use of sensory
Fig. 1 – Functional neuroanatomy of smooth pursuit ocular movements. Sensory information is projected to the primary visual cortex (IPVC), with limited response capacity, which projects to the occipital-temporal-parietal junction ([O-T-P], enhanced in light gray), which is sensitive to movement. From there, the signal is sent to the frontal visual area (FVA), the parietal visual area (AVP) and to the Pontin (P). In addition to the FVA, other areas related to frontal control of smooth ocular pursuit are the supplementary frontal visual area (SFVA) and the dorsolateral cortex (DLC). The dark gray areas indicate the frontal areas related to planning, learning and predicting trajectories. The frontal visual areas also have projections toward the Pontin from where the information is sent to the cerebellum for modulation and from there back to the front lobe.

The next phase (sustained pursuit), in which the speed of the eye must match that of the target, depends on the visual feedback provided by the object and the predicted acceleration-trajectory. Minor errors in said pursuit are corrected with saccadic movements. Cognitive prediction mechanisms are crucial for cortical control of eye movements when pursuing targets with reliable paths.

Ocular smooth pursuit alterations involve difficulties in processing information about the environment and therefore could be related to erroneous interpretations of events.

Fig. 1 illustrates a scheme of the neuroanatomy of smooth pursuit movement. The information on retinal movements is projected through the lateral geniculate nucleus to the primary (striate) visual cortex. The neurons of said cortex have a limited ability to respond to moving targets but project to the occipital-temporal-parietal junction which is sensitive to moving stimuli. The visual signals are sent from the occipital-temporal-parietal association area to the front and visual area that is in charge of the motor control of the pursuit, but particularly with initiating and predicting the trajectory.

Other frontal areas involved in controlling ocular pursuit are the frontal visual supplementary and the anterior cingulate areas, related to trajectory learning.

The dorsolateral prefrontal cortex and the parietal ocular region are involved in selecting and following-up targets (the dorsolateral prefrontal cortex is related to working memory). Both the striate cortex and the frontal visual areas have projections toward the Pontine nuclei, from where visual information is relayed to the cerebellum for modulation and sent back to the frontal lobe. Basal ganglia are mainly related with saccadic movements.

Even though ocular pursuit is generally voluntary, it is related to the perception of objects moving in the retina and processes that induce eye movement without active control. It is also necessary to predict the direction of the target, which depends on extraretinal functions other than simple perception, including attention. Cognitive (i.e., extraretinal) mechanisms could also be responsible for generating anticipative ocular movements when the previous learning (experience) produces an expectation about the path the target will follow. Cognitive functions related to smooth pursuit are those related with frontal cortical activity or frontal-parietal circuit and involve attention, selection, expectation, working memory, prediction and detection of changes.

To some extent, the neuroanatomy involved in smooth pursuit overlaps the brain areas related to schizophrenia. That is, some characteristics of smooth pursuit and specific characteristics of the disease partially share their anatomic substrate. Whatever it is that causes the functional alteration of said shared anatomic substrate (genes, environmental factors, interaction between both), could play a role in the complex causes of schizophrenia. In this disease, research has evidenced alterations in the cytoarchitecture of the front lobe as well as its connections with other areas, which causes patients to fail in cognitive flexibility, inhibition of responses to irrelevant stimuli, sustained attention and working memory, as well as motor-catatonic alterations.

**Evaluation of smooth pursuit movements**

Studying ocular movements (smooth or saccadic) in schizophrenia is simple for the patient, of short duration and minimally invasive. In addition, it does not depend on introspection capacities. Before carrying out the said study a foreign ocular examination is recommendable to discard disorders which could interfere with the evaluation thereof.

**Methods for measuring eye movements**

The simplest evaluation of ocular movements is through clinical assessment. Since the seventies, objective measurements are used such as EOG in which electrical potential differences due to changes in eye position are recorded by means of electrodes. However, the drawback of EOG is that it can produce noise, e.g. caused by blinking.

At present, an infrared detection method which follows the movement of the sclerocorneal limbus is commonly used. Alternatively, ocular movements recorded with a high-frequency camera can be quantified by reflecting a light projected on the cornea (the Hirschberg reflection). Other technologies are also available, such as special eyeglasses equipped with small cameras.
Smooth pursuit movement evaluation protocols

Evaluation can be global or specific. Global evaluation is qualitative (the researcher assesses the performance between poor and excellent) or quantitative (equipment that scores the numerical scales). Global evaluation methods are reliable but do not differentiate between pursuit or saccadic movements. Accordingly, global evaluation is used for screening ocular pursuit alterations.

Evaluation of performance for specific aspects of smooth pursuit range from exploring a broad range of alterations involving various substrates (physiological-anatomic-cognitive) up to the study of a specific endo-phenotype. In the former (exploratory work), the researcher must consider several protocols on the basis of their hypothesis whereas in the latter (specific studies) there should be a preestablished standard procedure.

There is a large number of possible parameter combinations, from predictable movement patterns up to variable redirection or acceleration patterns. For instance, targets with sinus, triangular or trapezoidal patterns of varying amplitudes can be used (Fig. 2). The moving targets can be concealed for a specific period of time or 2 different stimuli or sound distractions can be included in order to study extraretinal features such as prediction abilities or attention.

Currently, research is focused on identifying the specific features of slow pursuit which are endophenotypes of schizophrenia. In this area, specific measurement methods are of choice, such as concealing the target to assess prediction capacities. The radius between the speed of the eye and the target (gain) is another well-accepted parameter because it can measure a value between zero and one which, in ideal conditions, would be one. There are at least 2 different times to evaluate gain, which corresponds to the initiation and the sustainment phases.

Predictive smooth pursuit movements are of particular interest for schizophrenia as they require the integration of retinal perception with the internal representation of the movement of the target (extraretinal component) in order to determine where the target will be located at a specific point in time. Through functional resonance it has been determined that the posterior parietal cortex, the complementary visual and frontal visual are related to said extraretinal component.

In addition, the number and characteristics of non-smooth pursuit movements such as saccadic movements can be quantified.

Epidemiology of smooth pursuit eye movements in relation to schizophrenia

A meta-analysis of 39 studies on smooth pursuit eye movement alterations in patients with disorders within the range of schizophrenia was published in 2008. Said studies controlled variables such as pharmacological treatment or consumption of nicotine. According to said report, the difference between healthy controls and patients is that the latter have more global failures (effect size > 0.6; p < 0.01). In addition, 8 out of 12 specific pursuit movement alterations were found more frequently in patients than in controls, with larger effect sizes for gain during the sustainment phase (effect size > 0.85; p < 0.001). The small number of studies evaluating trajectory prediction capacity in patients with schizophrenia included in said meta-analysis demonstrates a global tendency toward association, which indicates the need to explore along these lines in greater depth.

In what concerns discriminating capacity, 65% of schizophrenia patients and healthy controls were correctly classified on the basis of the score for overall performance during smooth pursuit movements. In addition, 63% of their first-degree relatives (with a high risk of contracting the disease) and controls were also correctly classified, which supports the hypotheses of smooth pursuit alterations could be used for screening individuals at-risk of contracting schizophrenia (together with other variables such as minor physical anomalies or some neuropsychological or personality disorders) (see Studies in Patient Families).

Clinical characteristics of schizophrenia and smooth pursuit movements

Studies on clinical characteristics of schizophrenia in relation to smooth pursuit movements have the drawback of having used different scales for the clinical assessment of the disease as well as varied protocols for quantifying movements. Even so, it can be said that the severity of the disease (according to the Brief Psychiatric Rating Scale) is not related to smooth ocular pursuit alterations. On the other hand, more research is required to confirm whether patients with negative symptoms (such as affective flattening) or positive symptom predominance (such as hallucinations or delirium) do not exhibit more alterations in smooth pursuit eye movements. It is also necessary to study the degree in which ocular pursuit movements hinder the performance of patients in work or sport activities.

Smooth pursuit eye movements are related to a range of cognitive processes and schizophrenia exhibits cognitive deficits as well as eye movement alterations. However, establishing an association between neuropsychological and smooth pursuit eye movement alterations in schizophrenia...
patients has proved to be an elusive task. This could be explained due to the variability of the studies in what concerns the segregation of slow pursuit components.\textsuperscript{33}

Effect of drugs on smooth pursuit ocular movements

Generally, many psychotropic drugs have a deleterious effect on smooth pursuit ocular movements as a result of their sedative action. Other psychoactive drugs without sedative effects such as serotoninerics, methylphenidate or nicotine do not worsen pursuit movements and can actually improve their execution.\textsuperscript{34,35}

The adverse consequences of non-stimulating drugs maintain their validity in the scope of those used for treating schizophrenia. Smooth pursuit ocular movements worsen with oral antipsychotics. This deleterious effect increases with long-term use and is higher with second-generation antipsychotics. There is a dissociation between the clinical response to treatment and the quality of smooth pursuit ocular movements and therefore these movements are not recommendable to assess the efficacy of available antipsychotics, although they could be useful for developing new drugs with different action mechanisms.\textsuperscript{34,35}

Nicotine improves performance in smooth pursuit ocular pursuit of objects in patients with schizophrenia.\textsuperscript{36} This is important because the nicotine system is related to the modulation of sensory stimuli transmitted from the heteromodal association areas (such as posterior and frontal parietal cortex) to the hippocampus, which involves implications in perception, learning and the interpretation of events.\textsuperscript{8}

Smooth pursuit ocular movements in other disorders

In addition to schizophrenia there are other entities such as affective disorders, obsessive-compulsive disorder (OCD) or autism which exhibit functional alteration in frontal circuits. Accordingly, it is worthy to determine whether patients with these disorders exhibit alterations in smooth pursuit movements because in addition it could give an idea about the specificity thereof in schizophrenia. Unfortunately, data on other disorders apart from schizophrenia are scarce and contradictory.\textsuperscript{45}

Some but not all studies suggest that affective patients (uni-or bipolar) and to a lesser extent their relatives exhibit alterations in smooth pursuit of ocular movements.\textsuperscript{14,46–48}

In 2011, Jaafari et al. reviewed 33 published articles on various types of ocular movement alterations in patients with OCD and referred that obsessive patients exhibit slight alterations in pursuit movements when following targets moving at high speed. According to these authors, it is necessary to research in greater depth the relationship between ocular movements and OCD by studying specific aspects of smooth pursuit ocular movements.\textsuperscript{49}

Apparently, individuals with autism exhibit alterations in ocular pursuit movements although data are not sufficient to draw conclusions.\textsuperscript{50,51} Ocular movements (both smooth and saccadic) have also been studied in other disorders which begin in childhood such as attention deficit disorder or dyslexia, but in general researchers have not taken into account that the majority of children with a psychiatric disorder do not have only one disorder\textsuperscript{52,53} which means that information on the subject is not sufficiently reliable.\textsuperscript{53}

Parkinson and Huntington diseases can be associated to eye movement alterations. In contrast with schizophrenia, in these diseases saccadic movement alterations are prominent. For instance, Huntington’s disease patients frequently exhibit the impossibility of suppressing the reflex of quickly gazing at the stimuli which appears all of a sudden.\textsuperscript{54,55}

Smooth ocular movement alterations have an effect in information processing and are related to the interpretation of events.\textsuperscript{4} This task involves the entirety of neuronal pathways that include frontal areas related to initiating, sustaining and predicting the trajectory of objects.\textsuperscript{15–14}

Alterations in the ability to predict the trajectory of objects could be highly characteristic of schizophrenia and is highly inheritable, which makes it a good candidate for becoming the endophenotype of the disorder.\textsuperscript{41,44}

Smooth follow-up deficit worsens with antipsychotic drugs due to the sedative effect. These movements are not

Studies in patient families

Studies in families are very valuable for assessing the possibilities of inheriting complex diseases like schizophrenia. They are also useful to assess whether specific biological characteristics are present in subjects at risk of contracting a disease.\textsuperscript{37} In addition, these studies can serve to define whether a biomarker can be considered as an endophenotype of a disorder, i.e., if it could be related to a specific genetic profile. The identification of endophenotypes is useful in multifactorial diseases such as schizophrenia because the pathway between the genetic susceptibility and final clinical expressions is generally complex.\textsuperscript{56}

The study of heritability in healthy twins demonstrates that genetic influence is important in smooth pursuit movements. Global performance alteration matches are greater in homozygote (61%) than in heterozygote twins (26%).\textsuperscript{39}

In a systematic review on various ocular movements alterations in families of schizophrenia patients, Calkins et al. (2008) found that relatives exhibit more global smooth pursuit ocular movement alterations when compared with controls. Relatives of patients also exhibit more difficulties to maintain speed during the sustainment phase.\textsuperscript{40}

Hong et al. (2006) found that families of schizophrenia patients tend to exhibit alterations in the predictive feature of smooth pursuit.\textsuperscript{41} The heritability of this characteristic makes it an interesting candidate for being singled out as the endophenotype of the disorder. In this regard, ocular smooth pursuit alterations have been related with the Val158Met substitution of the catechol-O-methyltransferase gene. Said substitution is associated to alterations in executive functions and in working memory.\textsuperscript{8,42,43} Considering all the above, it has been proposed that smooth pursuit ocular movement alterations indicate a deficit in the frontal prediction capacity of patients with schizophrenia.\textsuperscript{44}
recommendable for assessing the efficacy of currently available antipsychotics.\textsuperscript{34}

The identification of specific aspects of smooth pursuit ocular movements which could serve as endophenotypes for schizophrenia will enable studying the relationship of smooth pursuit alterations with clinical characteristics such as positive and negative symptoms, minor physical anomalies, neuropsychological deficits, and disability at work and sports, among others, in the context of the disease.\textsuperscript{8,56}

\section*{Conflict of interests}

No conflict of interests has been declared by the authors.

\section*{References}


