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Computational models of eye movements and their application to schizophrenia

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Patients with neuropsychiatric disorders, in particular schizophrenia, show a variety of eye movement abnormalities that putatively reflect alterations of perceptual inference, learning and cognitive control. While these abnormalities are consistently found at the group level, a particularly difficult and important challenge is to translate these findings into clinically useful tests for single patients. In this paper, we argue that generative models of eye movement data, which allow for inferring individual computational and physiological mechanisms, could contribute to filling this gap. We present a selective overview of eye movement paradigms with clinical relevance for schizophrenia and review existing computational approaches that rest on (or could be turned into) generative models. We conclude by outlining desirable clinical applications at the individual subject level and discuss the necessary validation studies.

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Introduction

Eye movements represent easily measurable behavioural responses which provide rich information about latent (hidden) cognitive processes — such as perceptual inference, learning and decision-making — which are of central interest for disease theories of psychiatric disorders. Additionally, many psychiatric disorders are accompanied by pronounced eye movement abnormalities (for reviews see [1–3]). Together with the practical ease of data acquisition, this makes eye movements of great interest for translational and clinical applications in psychiatry. However, the wealth of existing experimental findings has not yet been translated into diagnostic tools for clinical practice. For example, while a general deficit of smooth pursuit eye movements (SPEM) in patients with schizophrenia allows for a nearly perfect separation of patients from healthy controls [4], this does not constitute practically relevant progress: the diagnosis of schizophrenia is not a clinical problem; and the diagnostic label 'schizophrenia' does not allow for patient-specific predictions due to the heterogeneous nature of this disorder [5].

One strategy to address this is computational psychiatry [6,7] which strives for understanding the cognitive and physiological underpinnings of aberrant behaviour by using mathematical models and, ultimately, translate these findings into clinical practice. The ongoing application of this approach to neuroimaging data has highlighted the importance of so-called 'generative models' (Figure 1) for clinical applications [8]. This is due to three main features (for detailed discussion and review, see [9]): generative models enforce mechanistic thinking about how observed data could have been caused; they deal with uncertainty (about model structure and parameters) in a principled way and thus provide a natural fundament for formalizing differential diagnosis; and they can be combined with unsupervised approaches, such as clustering, for detecting mechanistically distinct patient subgroups in heterogeneous disorders (e.g. [10]). Here, we review emerging generative models for eye movement data and discuss their possible role for translational research in psychiatry, with a focus on schizophrenia.

While there is evidence for disturbed eye movements in schizophrenia in many different tasks, historically, SPEM [2] and voluntary control of eye movements in antisaccades [1] have been the most widely used eye movement paradigms in schizophrenia. More recently, theories highlighting failures of inference and predictions in schizophrenia [11–13] have triggered an additional line of research focusing on corollary discharge (CD) during eye movements. The following sections revisit these paradigms, describe a selection of existing computational models, and hint at possible developments towards generative models.

Generative models for eye movements

Generative models represent a probabilistic mapping from latent (unobservable or hidden) variables θ (e.g. the parameters of a system) to observed data. This

Figure 1

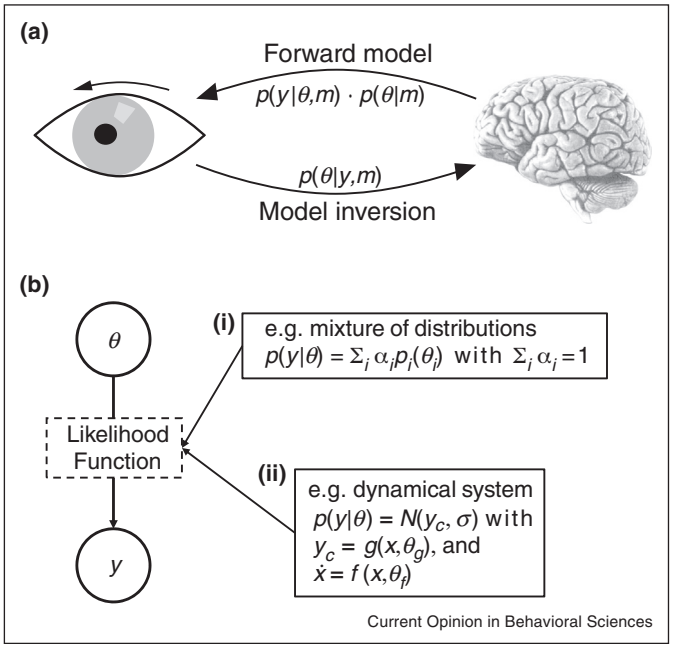


Illustration of generative modelling. **(a)** Schematic illustration of generative modelling. A generative model for eye movements describes how a latent (unobserved or hidden) neurophysiological process produces eye movements, for example, pursuit traces or reaction times (RTs) for saccades. The forward model m defines the joint probability of data (here: eye movement measurements) and model parameters; this results from the product of the a prior distribution $p(\theta|m)$ of model parameters and a likelihood function $p(y|\theta,m)$ that encodes the probability of the observed data y given the parameters θ. Model inversion corresponds to inferring the posterior probability of the parameters, given the data, $p(\theta|y,m)$. **(b)** Representation of the generative model in (a) as a graphical model. The likelihood specifies the mapping from parameters to data and thus encodes a particular proposal how the observed data were generated. A simple phenomenological approach is to assume that the data result from a weighted combination of distributions $p_i(\theta_i)$ with mixing weights a_i (panel **i**), Biologically more interpretable models can be constructed by choosing a hierarchically formulated likelihood, where hidden states x evolve according to a biophysically motivated dynamical system f (with parameters θ_f) and are linked to data through an observation function g (with parameters θ_g) and measurement noise ε. See panel **ii**. The data is assumed to be normally distributed around the predicted trace y_c with standard deviation σ. This formulation is known as dynamic causal modelling (DCM).

mapping is specified by two components (Figure 1; [14]): First, a prior distribution $p(\theta)$ defines the range of parameter values which are plausible a priori. Second, a likelihood function $p(y|\theta)$ specifies a mechanism by which measured data y are generated probabilistically, given the parameters. The product of prior and likelihood yields the joint probability of data and parameters. Models of this sort are called 'generative' because one can generate synthetic data, by feeding samples from the prior into the likelihood function.

The specific mechanism proposed by the likelihood function is one of the defining features of a particular generative model; for eye movements, this can take very different forms. A simple approach is to explain saccadic RTs phenomenologically, as a mixture of distributions (Figure 1, panel i). By contrast, biologically more interpretable models can be constructed by choosing a hierarchically structured likelihood function, where hidden (neuronal or computational) states evolve according to a biophysically motivated dynamical system f and are linked to data through a static observation function g with measurement noise σ (Figure 1, panel ii). This hierarchical formulation underlies a special class of generative models, so-called dynamic causal models (DCMs) [15]. It is possible, in principle, to extend existing dynamical models of eye movement control to full generative models. This requires rendering them fully probabilistic by introducing priors on the parameters and adding a probabilistic observation function.

For all generative models, statistical inference on the model parameters can be performed by computing the posterior probability of the parameters, given the data, using Bayes' rule (model inversion). The numerical feasibility of model inversion depends on the complexity of the model. Thus, restricting generative models to a limited number of unknown parameters is important for practical utility. Generative models also offer a principled approach for model comparison, based on the model evidence $p(y|m)$, which represents a principled measure for the trade-off between accuracy and complexity of a model.

This allows one to compare the relative plausibility of alternative dynamical system mechanisms [16] that might underlie observed eye movements.

Smooth pursuit eye movements

Among the different types of eye movements, studies of SPEM have the longest experimental tradition in schizophrenia research [2]. Patients with schizophrenia show a general deficit in SPEM which distinguishes them from healthy controls almost perfectly [4]. In addition, compared to controls, patients show reduced ability to predict a target's trajectory during occlusion [17]; at the same time, patients with schizophrenia are superior in tracking targets with unpredictable changes in their trajectory [18]. Both phenomena can be explained by the same putative mechanism, that is, reduced efficacy (precision) of predictions during perceptual inference [12,19]. This hypothesis is difficult to test with traditional mathematical models of SPEM, which have typically taken the form of dynamical systems with a focus on questions of gain control and less on prediction [20,21]. More recently, in order to account for predictions, Kalman filtering [22] and models based on the notion of 'predictive coding' (a hierarchical inference scheme where each level predicts the state of the next-lower level below and updates its predictions proportional to precision-weighted prediction errors; [23,24]) and 'active inference' (where actions are selected in order to fulfil sensory predictions) [19,25•] have been introduced to smooth pursuit. For example, the generative model introduced by Adams and colleagues [19,25•] is a dynamic causal model (DCM; Figure 1) that provides a physiological implementation of predictive coding principles during SPEM (Figure 2). This model has found application to empirical SPEM data from healthy volunteers [25•] and for simulating the empirically observed SPEM anomalies in patients with schizophrenia, including their superior performance in tracking target trajectories with unpredictable changes [19]. A recent combined SPEM and magnetoencephalography (MEG) application of this model demonstrated how a precision parameter of the pursuit model can be linked to recurrent connectivity in visual areas and inferred from MEG data [26••]. An important next step will be to apply this model to empirical data from patients, and to examine whether its parameter estimates allow for clinically relevant predictions in individual patients (see below).

Voluntary control of eye movements — the antisaccade task

In the antisaccade task, participants are required to withhold a reactive eye movement to a peripheral target and instead perform a saccade to the opposite location from the current fixation point. On this task, patients with schizophrenia show increased error rates (failures of withholding the reactive saccade) and increased latencies compared to healthy controls [1]. It is controversial whether this is due to a failure of inhibitory control or a failure of initiating the endogenous movement plan for the antisaccade [1,27]. This debate is mirrored by two models that have been applied to antisaccades in humans [28••,29•]; see Figure 3. In the LATER (Linear Approach to Threshold at Ergodic Rate) model [29•], the reactive prosaccade is stopped by a stop signal that races against the prosaccade; here, antisaccade errors are due to failure of inhibitory control. In the Cutsuridis model [28••], a competition between two alternative saccadic plans — prosaccade (error) and antisaccade (correct response) — determines the resulting saccade. The two models differ considerably in their implementation. The LATER model [29•] is a process model, which represents the evolution of a decision variable (essentially the log posterior odds ratio between two hypotheses) over time. It can be easily expanded into a full generative model of trial-wise reaction times (RTs), by formalizing its likelihood function [30] and specifying priors. The Cutsuridis model [28••], by contrast, specifies a detailed neuronal circuit within the superior colliculus whose activity determines RTs. So far, it has been used to simulate some of the deficits observed empirically in patients with schizophrenia [28••]. Using this model for inference from empirical data would require transforming it into a full generative model, possibly under appropriate simplifications.

Other models for antisaccades range from simple distributional models [31] to elaborate neurophysiological models of layered cortical units [32] or cortico-basal ganglia loops [33]. While offering direct links to physiology, the last two model types appear presently too complex to be transformed into generative models that could be inverted.

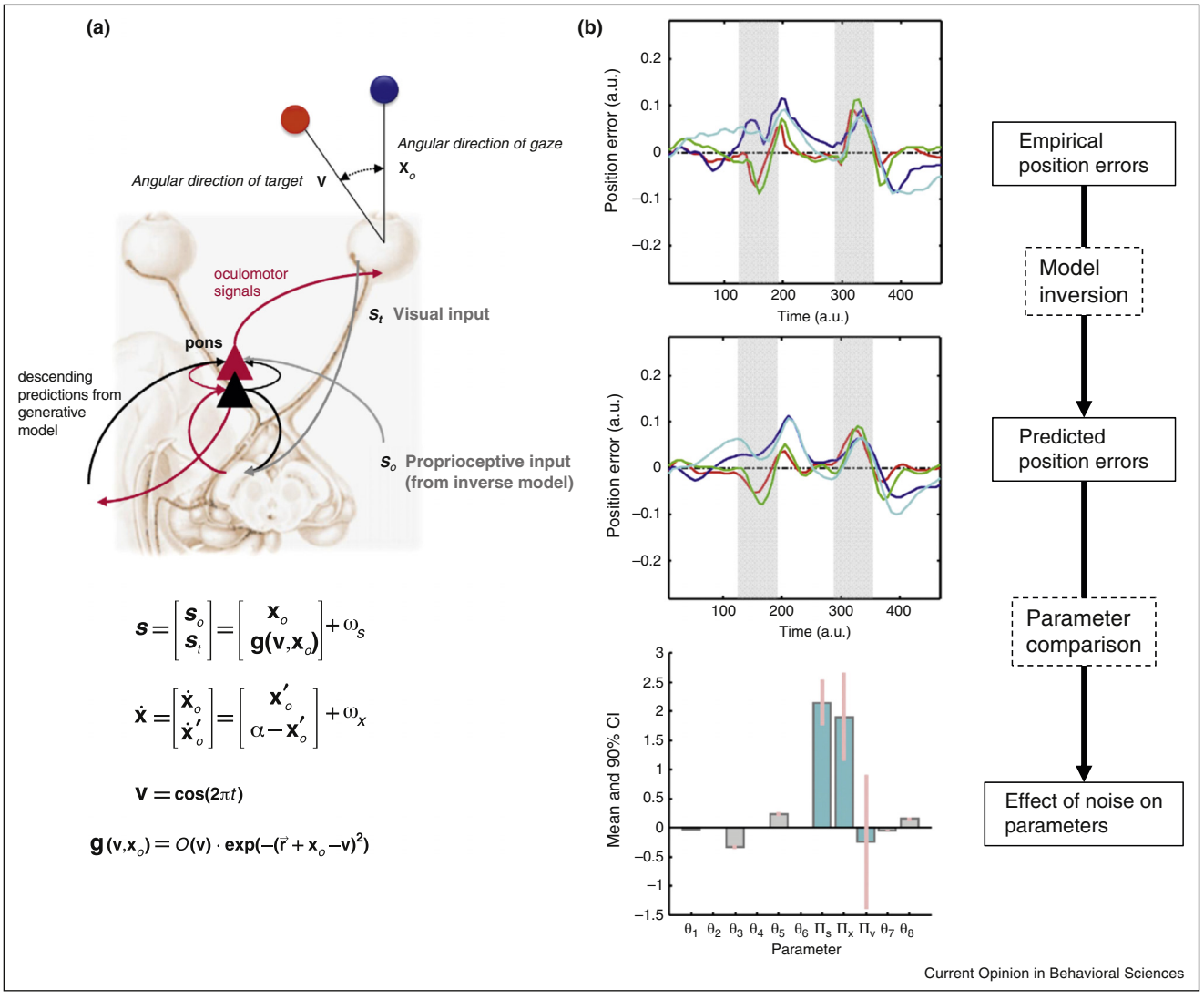
In summary, although fully generative models of antisaccades still need to be developed, a number of computational models exist which can be used as starting points.

Corollary discharge for saccadic eye movements

Corollary discharges (CD) are neuronal signals from executive (motor) areas that inform sensory areas about upcoming action [34] and thus enable a prediction about the changes in sensory inputs that result from one's own action. Influential hypotheses postulate that a failure of CD causes 'first rank' symptoms in schizophrenia: hallucinations and delusions of control (the sensation that an external force controls one's movements or thoughts) [11–13]. The neurophysiology of CD for saccadic eye movements has been extensively studied in primates (for a review see [34]) providing important constraints for models of CD. Figure 4 summarizes three eye movement tasks — double step saccades, perisaccadic change detection and saccadic adaptation — in which CD plays an essential role.

Several recent studies using these tasks have provided evidence for impaired CD during saccadic eye movements

Figure 2



A dynamic causal model of SPEM [25•], with state equations motivated by the notion of 'active inference' [19]. **(a)** Summary of the model's state equations for the generative process. Here, ***v*** is the angular direction of a target moving on a sinusoidal trajectory. Sensory input *s* includes proprioceptive (s_0) and retinal (s_t) input. Retinal input is modelled with Gaussian receptive fields (second term of observation function ***g***) and includes an occluder function $O(\boldsymbol{v})$ that turns retinal input on or off, depending on when the target is behind an occluder. ***x*** describes the hidden states, that is, angular position $\boldsymbol{x_0}$ and velocity $\boldsymbol{x}'_0$. Changes in position are driven by angular velocity; changes in velocity are driven by action (*a*). Both hidden states and sensory inputs are noisy, where the Gaussian noise is indicated by $\boldsymbol{\omega_s}$ and $\boldsymbol{\omega_x}$. For more details, see [25•]. **(b)** Top: Average empirical position errors (deviation of angular direction of gaze from target: $x_0 - v$) for four conditions (red: slow smooth target, blue: slow noisy target, green: fast smooth target, cyan: fast noisy target). Model inversion (parameter estimation) proceeds using these traces. Model fit is visible from predicted position errors (middle panel). Finally, comparison of posterior parameter estimates between noisy and non-noisy conditions allows for estimating an effect of sensory noise on model parameters (bottom).
Figure adapted from [25•] with permission (*Creative Commons Attribution License* (*CC BY*)).

in patients with schizophrenia. Using an error correction version of the double step paradigm, Thakkar *et al.* [35•] showed that CD for saccades is disrupted in patients with schizophrenia and is related to the severity of psychotic symptoms [36••]. Furthermore, both a stronger mislocalization in perisaccadic flash detection [37•] and reduced saccadic adaptation [38,39] have been reported in individuals with schizophrenia. While the latter was mainly interpreted as a cerebellar deficit by the authors, there is strong evidence that CD-based prediction errors play an important role in saccadic adaptation [40], with the superior colliculus as a crucial source of these error signals for adaptation [41].

To the best of our knowledge, no model of the double step paradigm exists so far. For perisaccadic change

Figure 3

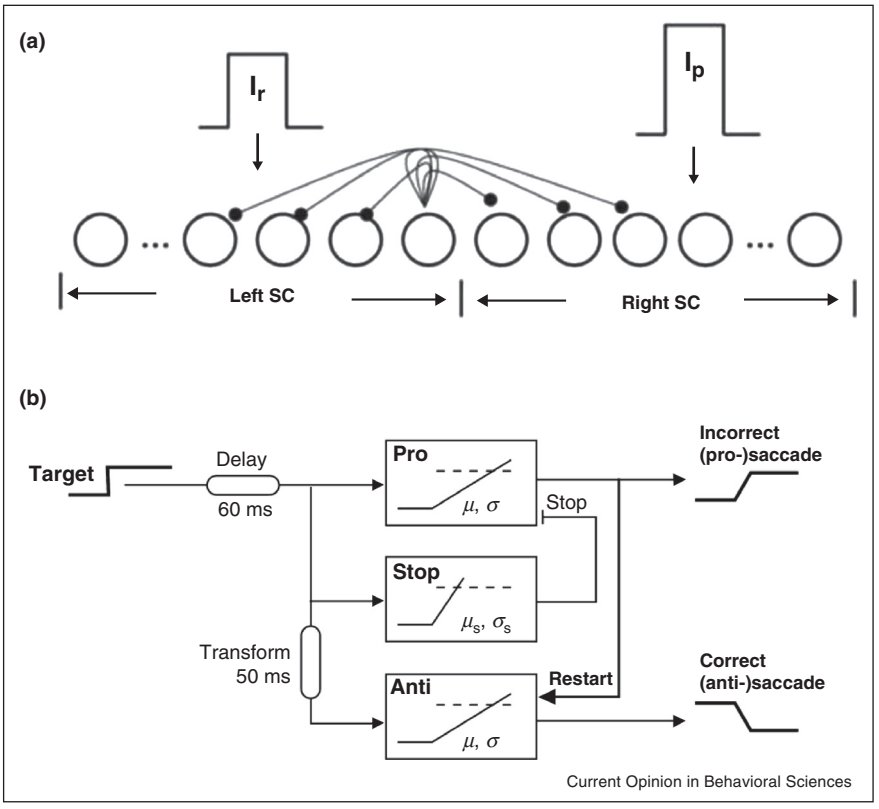


Illustration of two models of the antisaccade task. **(a)** Superior colliculus (SC) model by Cutsuridis *et al.* [28••]. A circuit of neuronal populations which code for different eccentricities along the horizontal axis and represent a competitive neural network within the SC. Two unspecified inputs, presumably of cortical origin, drive the prosaccade (reactive input I_r) and antisaccade (planned input I_p). Given these two inputs and some assumptions about differences in neuronal time constants between the two colliculi on the prosaccade and antisaccade side, the model reproduces a variety of findings from the antisaccade literature, including corrective saccades after errors. Figure reproduced from [28••] with permission *(Creative Commons Attribution License (CC BY)).* **(b)** The LATER model for antisaccades [29•] is based on three race-to-threshold units. On an antisaccade trial, prosaccade and stop units start a race, followed by the antisaccade unit with a delay. If the stop unit reaches threshold first, the prosaccade race is cancelled and the antisaccade unit defines the RT. If the prosaccade unit reaches threshold before the stop unit an error occurs, and the antisaccade unit is reset to trigger a corrective saccade.
Reproduced from [29•] with permission.

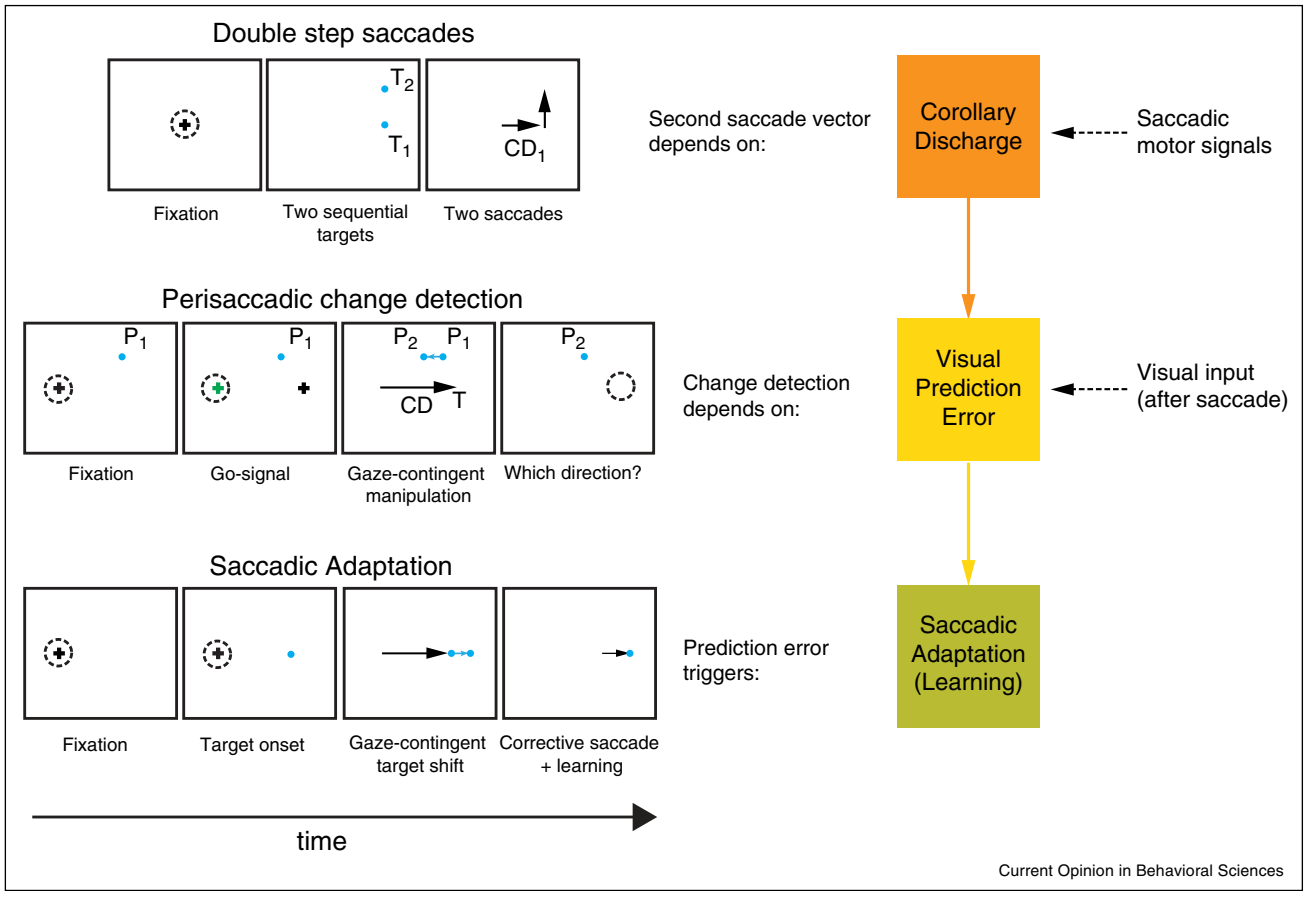
detection, Hamker and colleagues [42,43] have developed a detailed model of interactions between topographic cortical maps which could potentially be simplified to provide a generative model for perisaccadic change detection. Finally, saccadic adaption can be modelled by a simple learning rule [44] that is structurally equivalent to standard update equations in generative models of choice behaviour [45]. Models of this type can explain a range of observations for saccadic adaptation in monkeys [46]. Application of this or similar models to empirical data on saccadic adaptation from patients with schizophrenia [38,39] would be straightforward but is outstanding so far.

In summary, with the exception of saccadic adaption, generative models for CD in eye movements still need to be developed.

Additional directions

In this section, we briefly outline other eye movement paradigms with relevance for schizophrenia and generative modelling. Similar to SPEM, *visual scene scanning* almost perfectly distinguishes between patients and controls [4]. Generative models of scan paths can be derived from Bayesian models of attention [47] or active inference [48]. In addition to the scan paths, investigating fixational eye movements (small eye movements during fixations) would be of high interest. A recent study found that fixation stability during free viewing was the single most informative parameter for classification of schizophrenia patients [4]. Models of fixational eye movements are readily available [49,50] and have been fitted to data of healthy subjects using grid search [50]. It would be straight forward to extend these models to a fully generative framework. Second, *reading eye movements* are abnormal in patients [51]. Mathematical

Figure 4



Saccadic eye movement tasks that involve CD. Double step saccades require two consecutive saccades to briefly flashed targets T_1 and T_2. Both targets vanish before the first saccade is initiated from the fixation point F. In the absence of any visual target, the second saccade needs to be pre-computed as $FT_2 \rightarrow -CD_1 \rightarrow$, where $CD_1 \rightarrow$ is the vector represented by the corollary discharge for the first saccade. Hence, in this task, CD is only used for motor planning, not for predicting visual input. In the perisaccadic change detection task, a visual target at position P_1 is moved to position P_2 during the saccade. After landing, the expected retinal position of the target is $FP_1 \rightarrow -CD \rightarrow$, which has to be compared with the true retinal position $TP_2 \rightarrow$. Here, $CD \rightarrow$ is a vector representation of the corollary discharge and T the landing position of the saccade. In this setting, CD is used for the prediction of visual input after the saccade and thus enables computing a prediction error if target position changed. Finally, in saccadic adaption the visual target is moved consistently on every trial. The resulting prediction error is used to adapt saccade magnitude over trials. The right panel illustrates the relations between tasks.

models of cognitive and lexical processes [52,53] are able to reproduce a wide range of eye movement data in reading. These could be simplified to result in fully generative models. Finally, patients with schizophrenia show abnormal cue-guided spatial attention (*Posner paradigm*; [54]). Vossel *et al.* [55] have used a generative model, a hierarchical Gaussian filter [45], to infer the mechanisms which govern variation of saccadic RTs under volatility (changes in the predictive strength of the cue). This task and model have subsequently been combined with pharmacological (cholinergic) stimulation [56•] and fMRI [57].

Prospects for generative models of eye movements in schizophrenia research

In this final section, we briefly outline future translational and clinical opportunities for (generative) models of eye movements, with a focus on the three main paradigms described above.

Translation from animal to human research

The three eye movement paradigms described above are strongly dependent on cortical–subcortical loops that involve the frontal cortex [58,59] and are likely altered in the schizophrenia spectrum [60,61]. Studies of these circuits in primates [34,62,63] provide anatomical and physiological data which are essential for the development of biologically realistic models in humans [32,33]. An important next step is to simplify and recast these models as generative models in order to allow for inference on pathophysiological mechanisms in human patients.

Computational phenotyping, differential diagnosis and clinical predictions

Schizophrenia is a heterogeneous spectrum disease, where identical symptoms can arise from different mechanisms across patients. For example, while many symptoms in schizophrenia can be understood as arising from a general deficit in perceptual inference [12], this could be due to different causes. For example, from a computational perspective, hallucinations could plausibly arise from deficient CD, overly tight/inflexible high-level priors, or attenuated/misplaced low-level prediction errors (cf. [64]). A battery of simple eye movement tasks which allow cross-comparing models representing these competing explanations would introduce a valuable tool for differential diagnosis to clinical practice. This requires two things: prospective clinical studies which evaluate the predictive validity of model-based differential diagnosis against relevant clinical outcomes, and statistical model comparison techniques. The latter can require computationally demanding sampling techniques for complex models but will increasingly benefit from dedicated open source software [65].

Computational assays of neuromodulation

Similar to model-based EEG or MEG [66], generative models of eye movements could become useful as computational assays for neuromodulatory action, such as the availability of a particular neuromodulatory transmitter. While some model-based work has focused on neuromodulatory effects on pupil size [67,68], the pronounced sensitivity of saccadic eye movements to neuromodulatory alterations [69] has found remarkably little exploitation so far. If generative models of eye movements allowed for establishing sufficiently sensitive and specific assays of neuromodulatory abnormalities, this could provide valuable guidance for treatment decisions, for example, when deciding between antipsychotic drugs with differential emphasis on dopaminergic and cholinergic mechanisms [70]. Again, this eventually requires prospective clinical studies; initially, however, pharmacological validation studies need to be conducted that test whether generative models of eye movements can detect specific dopaminergic or cholinergic manipulations in single subjects.

Conclusion

Computational modelling of eye movement data is a promising way forward in schizophrenia research, but also for many other neuropsychiatric disorders where eye movement deficits are observed. In particular, analogous to similar developments in computational neuroimaging [8], generative models of eye movements might enable inference on pathophysiological and/or pathocomputational mechanisms which underlie eye movement abnormalities in single patients. Single subject parameter estimates or model comparison could then enable clinically relevant applications for differential diagnosis, to predict treatment outcome or aid treatment choices, and estimate risk of relapse or transition to disease. A key challenge for the future will be to finesse existing and develop novel generative models for eye movements; the neurophysiological interpretability and clinical utility of these models must then be evaluated in pharmacological validation studies and prospective patient studies.

Conflict of interest statement

Nothing declared.

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