

Opinion

Oculomotor Prediction: A Window into the Psychotic Mind

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Psychosis – an impaired contact with reality – is a hallmark of schizophrenia. Many psychotic symptoms are associated with disruptions in agency – the sense that ‘I’ cause my actions. A failure to predict sensory consequences of one’s own actions may underlie agency disturbances. Such predictions rely on corollary discharge (CD) signals, ‘copies’ of movement commands sent to sensory regions prior to action execution. Here, we make a case that the oculomotor system is a promising model for understanding CD in psychosis, building on advances in our understanding of the behavioral and neurophysiological correlates of CD associated with eye movements. In this opinion article, we provide an overview of recent evidence for disturbed oculomotor CD in schizophrenia, potentially linking bizarre and disturbing psychotic experiences with basic physiological processes.

Oculomotor Probes of Agency Disturbances in Psychosis

Our sense of reality relies on the rapid perception and interpretation of our world. The brain’s ability to make predictions based on current context forms an integral part of shaping and adapting to reality: When we push a swing, we expect it to swing back, and – as adaptive systems – we are able to effectively adjust our responses accordingly [1]: we stop the swing or get out of the way. This simple example is illustrative of how biological systems exist in dynamic and symbiotic relationships with their environment. When a system is unable to exist in such a relationship, it is inherently impaired. It is notable that this relatively simple framework, termed **predictive coding** (see [Glossary](#)), is now being applied to the understanding of psychiatric illnesses in general [2], and **psychosis** in particular.

Psychosis evokes separation from reality and includes experiences like hallucinations (false perceptions) and delusions (irrational beliefs). An individual may hear a voice criticizing their appearance or be convinced that the government controls their mind through an implanted device. These are not illusions or vague notions – they are experienced as reality and are notoriously immune to evidence of the contrary. Acute psychosis occurs in many medical and psychiatric conditions and is sometimes considered ‘the fever’ of mental illness. In no disorder, however, is psychosis as enduring and profound as in **schizophrenia**. Schizophrenia is an epigenetic puzzle, a complex polygenic disorder whose etiological bases remain poorly understood. The world appears radically different to the schizophrenia patient, and this difference is the basis for the illness’ core characteristics.

Unsurprisingly, the notion of disordered prediction has featured prominently in mechanistic theories of psychosis [3–5]. These theories effectively argue that psychosis arises due to an

Trends

Psychosis, a defining feature of schizophrenia, is associated with profound disruptions in the sense of agency. A failure to predict the sensory consequences of actions may underlie these agency disturbances.

Predicting consequences of self-generated action relies on CD signals, ‘copies’ of movement commands that are sent to sensory regions prior to action execution.

The oculomotor system is a promising model for understanding abnormal CD in psychosis, building on significant advances in our understanding of the behavioral and neurophysiological correlates of CD associated with eye movements in humans and non-human primates.

A surge of recent evidence suggests disturbed CD associated with eye movements in schizophrenia, shedding light on the mechanisms of the symptoms that have been the most challenging to explain at the level of physiology.

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abnormality in forming or using stored regularities that structure and help us understand the environment. This abnormality leads to misinterpretations of sensory information and overinterpretation of random associations, thus potentially explaining both hallucinations and delusions [3]. More generally, it has been argued that these prediction disruptions cause a fragmented interaction with the external world and a disjointed self. Within this framework, psychosis can be explained by a failure in predicting both how external stimuli co-occur and the sensory consequences of actions. In this opinion piece, we argue that the oculomotor system provides an ideal framework for investigating the latter: Understanding how the brain anticipates the sensory consequences of movement provides a powerful model for understanding how these processes could go awry in psychosis.

The brain's mechanism for anticipating the sensory consequences of movement is remarkably elegant: 'copies' of motor commands – so-called **corollary discharge** (CD) signals – are used to form a prediction of the sensation expected from the self-generated movement (sometimes referred to as the forward model), which is then sent to sensory areas prior to or during movement execution (Figure 1A, Key Figure). When the actual self-generated sensation is consistent with the prediction, it can be largely ignored, sparing resources for information that does violate our predictions. Further, these predictions allow self-generated actions to be recognized as such: when the predicted sensation matches the actual sensation, we have a subjective experience of **agency**. Many psychotic experiences carry traces of an external misattribution of self-generated action, and a disturbance in CD has offered a plausible explanation for these agency-related phenomena across a range of sensorimotor domains (Box 1). Although CD disturbances provide the most compelling biological explanation for agency disturbances in psychosis, the evidence remains largely indirect.

Because the most robust evidence for CD in non-human primates and healthy human populations stems from studies of eye movements, we argue that the oculomotor system is an ideally suited model for testing hypotheses of abnormal CD in psychosis [6]. Indeed, eye movement impairments have been recognized in schizophrenia patients since the early 1900s [7], and CD-based predictions appear to underlie several sensorimotor functions including (i) the continuity of perception despite eye movements constantly displacing the retinal image [8]; (ii) the rapid production of accurate successive eye movements [9,10]; (iii) the precise tracking of moving stimuli [11]; and (iv) the adaptation of **saccade** commands in the face of consistent visual errors [12]. Objective and well-established paradigms that produce data with high signal-to-noise ratios have been developed to study each of these phenomena, and they allow clear and grounded predictions about the precise way in which CD should be evidenced behaviorally in clinical populations (Box 2).

In addition, an active research program investigating oculomotor prediction at the neurophysiological level has significantly advanced our understanding of CD associated with eye movements. We now know that certain types of **visual neurons** exhibit **predictive remapping**: they show vigorous visual responses even before the impending saccade brings a stimulus into their **receptive field** [13]. To do so, they must receive information about the time and target of the next saccade. A pathway between subcortical **saccade neurons** and cortical visual neurons appears to convey the CD signals necessary for these predictions via the mediodorsal thalamus (MD) [14–16]. The recent surge in publications investigating remapping and CD in the oculomotor system of individuals with schizophrenia underscores the utility of understanding abnormal prediction of self-generated actions and agency in psychosis through eye movement physiology [6]. This surge coincides with an expanding interest in understanding the role of thalamocortical interactions in psychotic disorders.

Glossary

Agency: the subjective experience that one controls the volitional action one produces.

Bipolar disorder: a disorder characterized by bouts of depression and elevated mood (mania). Psychosis is common during mood episodes.

Corollary discharge: 'copies' of motor commands that, rather than being sent to lower movement areas, are sent to sensory and higher processing areas.

Perceptual stability: the perception of the world as stationary despite the fact that eye movements incessantly displace the visual input on the retina.

Perisaccadic compression: a type of perisaccadic mislocalization in which visual stimuli flashed around the time of a saccade are perceived as closer to the saccade target than they actually were.

Perisaccadic mislocalization: the phenomenon that visual stimuli around the time of a saccade (before, after, or during) are perceived at a different location than the one in which they were presented.

Predictive coding: a framework for brain function, positing that the brain continually generates a model of the world based on current context and past experience and updates this model when the predicted and actual input do not match.

Predictive remapping: the finding that neurons in retinotopic brain areas start responding to a visual stimulus before an impending eye movement brings it into their receptive field (or, earlier than expected from reafferent processing).

Psychosis: a clinical phenomenon characterized by a loss of contact with reality.

Reafferent processing: processing of sensory input produced by the execution of one's own movement. In the case of eye movements, this input is primarily visual in nature.

Receptive field: the part of space in which stimuli alter a neuron's activity.

Retinal error: distance between a visual target and the location of gaze.

Retinotopic: organization of visual brain areas such that visual neurons in the brain have receptive fields encoding specific locations on the retina. Eye movements therefore

Box 1. Disturbed Corollary Discharge As a Mechanism of Psychosis

An altered sense of agency is at the heart of many psychotic symptoms – both hallucinations and delusions [90–92]. Passivity delusions, where the individual experiences thoughts or actions as under external control, provide a clear example. Similarly, auditory hallucinations are construed as subvocal or inner speech that is attributed externally. Models of sensorimotor control, which posit a system that predicts the sensory consequences of a movement command based on an internal signal (CD) [93], have been co-opted to explain these symptoms. CD is theorized to serve a function outside of the sensorimotor domain by supporting a subjective sense of agency over action. Sensory input that is consistent with prediction is tagged as self-generated. A breakdown in these CD signals may underlie the disturbed sense of agency in psychosis [91]: sensory events resulting from voluntary actions are unexpected and thus attributed externally. This notion conceptualizes thinking as an active motor process [94] to explain the external attribution of not only willful action but also of imagery and thoughts. Within this framework, the integrity of sensorimotor processing is central to a forward-fed normative construction of the self.

Indirect evidence for abnormal CD signals in psychosis exists in multiple sensory systems [95]:

Audition: Electrophysiological responses in auditory cortex to self-generated speech are attenuated in healthy individuals [96]. Individuals with schizophrenia show reduced modulation of auditory cortex during speech [96–100]. Furthermore, schizophrenia patients appear to correct speech errors based on auditory feedback rather than a CD signal from the phonetic plan [101].

Somatosensation: CD diminishes tactile responses to self-generated movement (indeed, we cannot tickle ourselves [102]); schizophrenia patients with passivity symptoms and auditory hallucinations show reduced attenuation of tactile responsivity to self-produced stimuli [103].

Proprioception: When healthy individuals are instructed to match the force they feel pressed on a lever, they consistently apply too much pressure, arguably because CD attenuates the sensation on the lever when they are actively producing the movement [104]. Individuals with schizophrenia are more accurate, consistent with altered CD [105]. In addition, they correct fewer erroneous joystick movements in the absence of external feedback [106,107].

Notably, other explanations for the experience of agency have been proposed. Cognitive theories posit that we experience agency when an action's outcome is consistent with our expectation [108]. Accordingly, goals, biases, and beliefs influence perceived agency. Inappropriate weighting of these different sources of information may contribute to altered agency experiences [109].

redirect the cells' receptive fields to new locations in the world.

Saccade: a rapid gaze shift redirecting the fovea (and thus, high-acuity vision) to a new location in space.

Saccade neuron: neuron that is silent during fixation and fires in relation to saccades to a particular location.

Schizophrenia: a neurodevelopmental disorder with genetic and environmental causes whose typical onset is in early adulthood. Diagnostic symptoms include psychosis, blunted affect and motivation, and disorganized thought and language. Cognitive and sensorimotor dysfunctions are also common.

Smooth pursuit: eye movements that keep a moving stimulus in the foveal region.

Spatiotopic: organization of visual brain areas such that visual neurons in the brain have receptive fields encoding specific locations in external space, independent of gaze location.

Thought disorder: symptom of psychosis in which disorganized thought becomes evident through disorganized language.

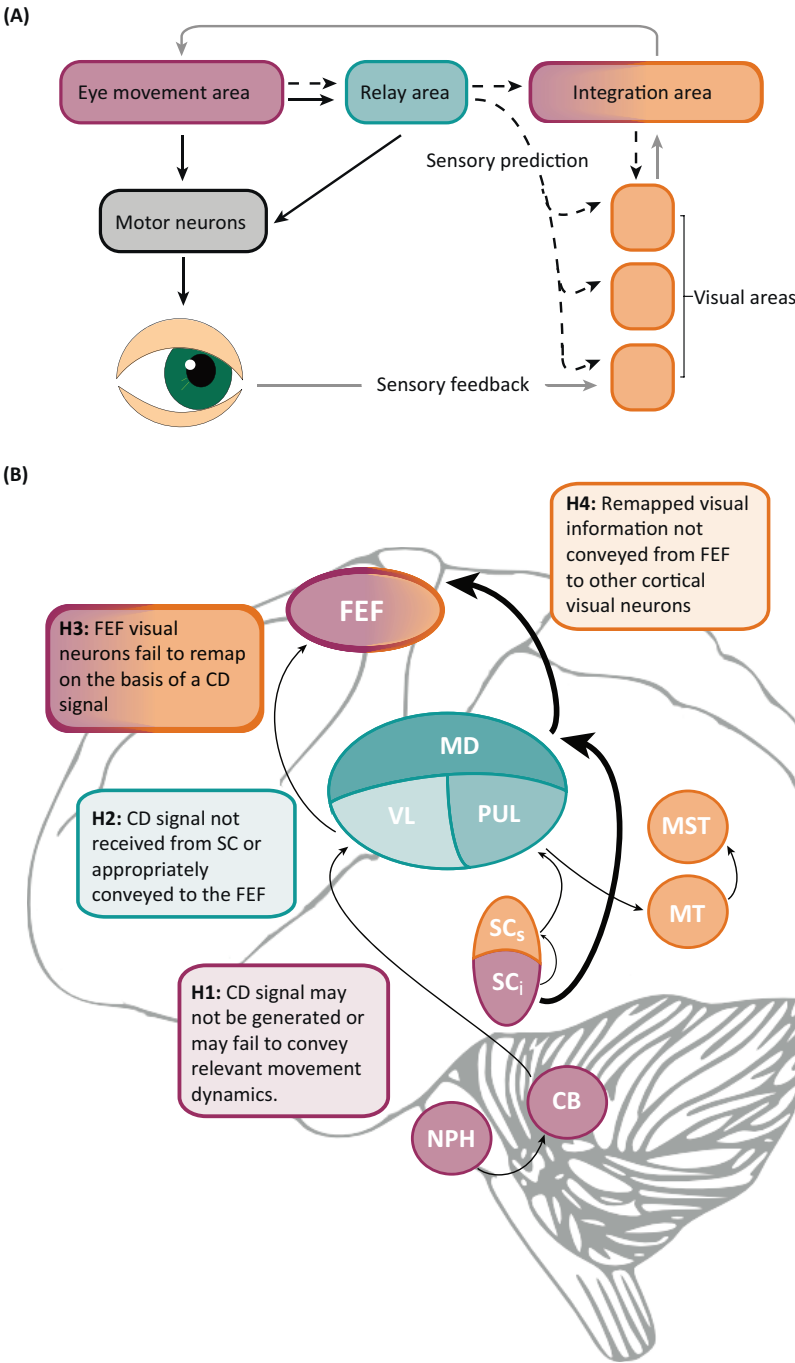
Visual neurons: neuron that fires in response to visual information in its receptive field.

Evidence for Disturbed Oculomotor CD in Psychosis

A number of behavioral paradigms have been developed to assess CD in the oculomotor system. Successful performance on these tasks relies on prediction of the (future) location of gaze, as **reafferent processing** is relatively slow. A putative CD signal subserves this prediction and informs both action plans and visual perception (Box 2). Patients with schizophrenia often show specific deficits on those tasks for both saccadic and **smooth pursuit** eye movements, suggesting an impaired or nonveridical CD signal that affects action plans (Figure 2) and visual perception (Figure 3). At the level of action control, individuals with schizophrenia show performance deficits consistent with altered CD on the double-step [17], smooth pursuit [18], predictive pursuit [19–23], and saccade adaptation [24–26] tasks. One exception here is in the rapid correction of saccades that are inconsistent with higher-level goals: for instance, fast corrections after errors in the antisaccade test are purported to rely on CD. Both impaired [27–29] and equal [30–33] antisaccade error correction latencies and rates have been reported. A notable aspect of these studies, however, is that visual feedback indicating an error (i.e., the visual target) was available to subjects. It is possible that error-correction impairments are only present when no external information is available to inform these corrections – that is, when they rely most heavily on CD. Indeed, a recent study using a modified double-step paradigm, where the second target was the cue to inhibit the response to the first target and saccade immediately to the second target [17], was conducted in complete darkness, and visual stimuli were flashed only briefly. Thus, no visual information could indicate that an error had been committed. Despite equal error rates and latencies in this task, individuals with schizophrenia made fewer and slower error corrections. In sum, evidence

Key Figure

Circuits Conveying a Corollary Discharge (CD) Signal in the Oculomotor System



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(See figure legend on the bottom of the next page.)

Box 2. Tapping CD Signals in the Oculomotor System at the Behavioral Level

CD signals convey information about an impending movement – its onset, the overall vector (direction and amplitude), or even the entire trajectory. In principle, therefore, any task in which performance is correlated to an eye movement in space and/or time is potentially informed by CD signals. A number of tasks aim at isolating CD-based predictions in perceptual and motor processes (in some cases, visual and proprioceptive signals are also potential sources of information).

In motor tasks, CD may influence movement execution or subsequent behavior. Predictive pursuit, for instance, occurs when the motion of a predictably moving target is interrupted (blanked or altered) for a brief moment [110] or stabilized on the fovea [74], eliminating the **retinal error** signal that would normally drive the movement. Thus, smooth tracking must rely on an internal prediction of motion and a corollary of the eye movement. In the saccadic system, the double-step task [9,10], in which two flashed stimuli cue a rapid sequence of two saccades, has become the litmus test of CD. To accurately land the second saccade, the oculomotor system must discount the vector of the first saccade from the encoded retinal vector of the second target. Similarly, CD signals are thought to enable fast corrections of erroneous saccades in paradigms requiring higher-level control (e.g., inhibition) of eye movements [111]. Finally, CD-based predictions drive saccadic adaptation: prediction errors experienced after previous saccades alter the metrics of future movements, and deviations from the intended trajectory may change saccades in midflight [112,113].

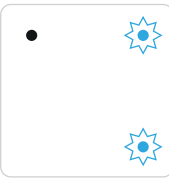
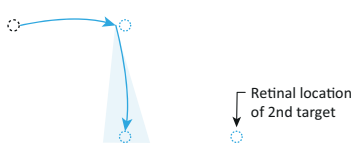
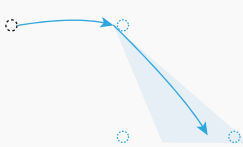
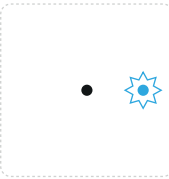

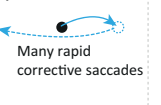

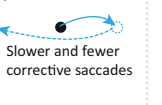

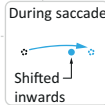
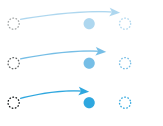
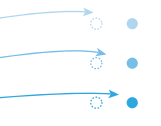
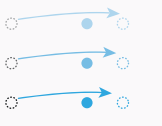
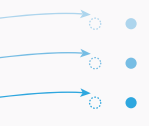
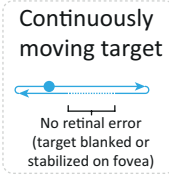
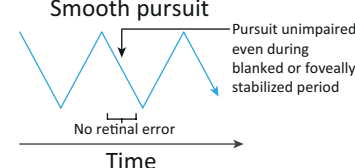
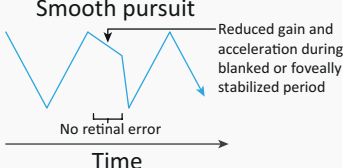



In perceptual tasks, correlates of a CD signal may be observed as soon as it is available – even before movement onset. Presaccadic shifts of attention are a case in point: these predictive boosts in visual performance are spatially selective to the saccade target and occur time locked to movement onset [114,115]. The most direct perceptual test of the precision of saccadic CD is the trans-saccadic localization task [37], in which the saccade target disappears with movement onset and reappears with a delay after saccade landing. This manipulation results in conspicuous **spatiotopic** apparent motion: the target is seen to jump from its origin to its new postsaccadic location with little (but systematic) error. Given the vastly different retinal locations at which the presaccadic and postsaccadic targets are seen (in the periphery vs. near the fovea), judging the direction of motion in this task must rely on a very precise CD signal [38].

from a range of experimental paradigms indicates that schizophrenia patients show impairments in using CD for action.

CD is also argued to support **perceptual stability** [34] in the face of disruptions in visual input generated by the moving eye. Accordingly, CD abnormalities in schizophrenia may also reveal themselves through altered perception during and immediately following eye movements. During smooth pursuit eye movements, CD fails to ensure visual stability of a static background image in those patients with the most severe psychotic symptoms [35]. Moreover, whereas in healthy controls estimation of the future location of a smoothly moving target is enhanced by smooth pursuit, schizophrenia patients fail to show that benefit, putatively due to abnormal CD [36].

For perceptual judgments around the time of a saccadic eye movement, the evidence is mixed. Schizophrenia patients show altered performance on the trans-saccadic localization task, in which the target is blanked during the saccade and reappears at a new location only after saccade landing [37,38]. This task relies on CD to inform the visual system of the vector of the

Figure 1. (A) Functional architecture. A motor command (solid black lines) issued from an area generating eye movements is sent to motor neurons controlling the eye muscles, either directly or via a relay node. An accompanying CD signal (dotted black lines) conveys information about the spatial and temporal dynamics of this movement to visual areas, either directly or via higher-order integration areas. Along with CD signals, visual and integration areas also receive sensory feedback regarding the retinal stimulation following the eye movement (gray line) and can compare the CD-based predictions with the actual sensory consequences (i.e., reafferent information). Although a relay node is not strictly necessary, it may facilitate the dissemination of the CD signals across multiple functional nodes and ensure that the timing of these signals is commensurate with the purpose it fulfills in the target sensory and higher processing areas. (B) Anatomical circuitry. Colors indicate mapping onto functions in panel A. Thicker arrows indicate pathways that have received more empirical support. CB, cerebellum; FEF, frontal eye fields; MD, mediodorsal nucleus of the thalamus; MST, medial superior temporal area; MT, middle temporal area; NPH, nucleus prepositus hypoglossi; PUL, pulvinar; SCi, intermediate layers of the superior colliculus; SCs, superficial layers of the superior colliculus; VL, ventrolateral nucleus of the thalamus.

Paradigm	Stimulus	Performance with intact CD	Predictions for impaired CD	Evidence [Refs]
(A) Double-step saccades		 Retinal location of 2nd target		+ [17]
(B) Response inhibition (antisaccade)		<div>Successful antisaccade</div>  <div>Erroneous prosaccade</div>  Many rapid corrective saccades	<div>Successful antisaccade</div>  <div>Erroneous prosaccade</div>  Slower and fewer corrective saccades	+ [17, 27–29] – [30–33]
(C) Saccadic adaptation	<div>Before saccade</div>  <div>During saccade</div>  Shifted inwards	<div>Inward</div>  <div>Outward</div> 	<div>Inward</div>  <div>Outward</div> 	+ [25,26] – [24]
(D) Predictive pursuit	<div>Continuously moving target</div>  No retinal error (target blanked or stabilized on fovea)	<div>Smooth pursuit</div>  Pursuit unimpaired even during blanked or foveally stabilized period No retinal error	<div>Smooth pursuit</div>  Reduced gain and acceleration during blanked or foveally stabilized period No retinal error	+ [19–23]
<div><div>Key:</div><div><div>● ○ Fixation target</div><div>● ○ Eye movement target</div><div> Briefly flashed stimulus</div><div> Impending eye movement</div><div> Executed eye movement</div></div><div>Evidence</div><div><div>+ positive (CD impaired)</div><div>(+) positive with caveats</div><div>– negative (CD unimpaired)</div></div></div>				

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Figure 2. Oculomotor Paradigms Used to Study the Role of Corollary Discharge (CD) Signals in Action. (A) Double-step task. Two targets flash to cue a sequence of two saccades. An accurate second saccade requires accounting for the metrics of the first saccade; patients show incomplete compensation. (B) Antisaccade task. After erroneous prosaccades, CD of the first saccade might play a role in rapidly executing a corrective saccade. (C) Saccade adaptation. The saccade target is displaced during the saccade. Provided an intact CD signal, consistent landing errors across trials result in a reduction of the saccade amplitude for inward adaptation, and an increase for outward adaptation. In patients, adaptation can be weakened or slowed. (D) Predictive pursuit. While tracking a predictably moving target, intact CD in the pursuit system facilitates smooth tracking during periods of zero visual error (e.g., due to blanking or image stabilization).

executed saccade. Altered CD, therefore, may cause impaired postsaccadic localization of visual targets in schizophrenia patients [39]. Two further studies investigated mislocalization of visual targets flashed around the time of a saccade, but their implications are unclear. One study found that the flashed target showed greater **perisaccadic mislocalization** in the direction of the saccade target in schizophrenia patients, consistent with a disturbed CD signal associated with a continuous readout of (the predicted) eye position during the saccade [40]. Using a model of perisaccadic mislocalization, the authors argued that the effect was consistent with a noisy, rather than delayed or absent, CD signal. A second study did not observe differences in perisaccadic mislocalization between schizophrenia patients and controls [25]; however, the localization target was flashed at only one delay following the saccade target, when large mislocalizations would not be expected [41]. Despite group differences in the shift toward the saccade target, no group differences in the compression toward the saccade target were observed [40]. Traditionally, **perisaccadic compression** has been thought to arise due to the perceptual effects of a transient CD signal associated with the saccade vector [42]. More

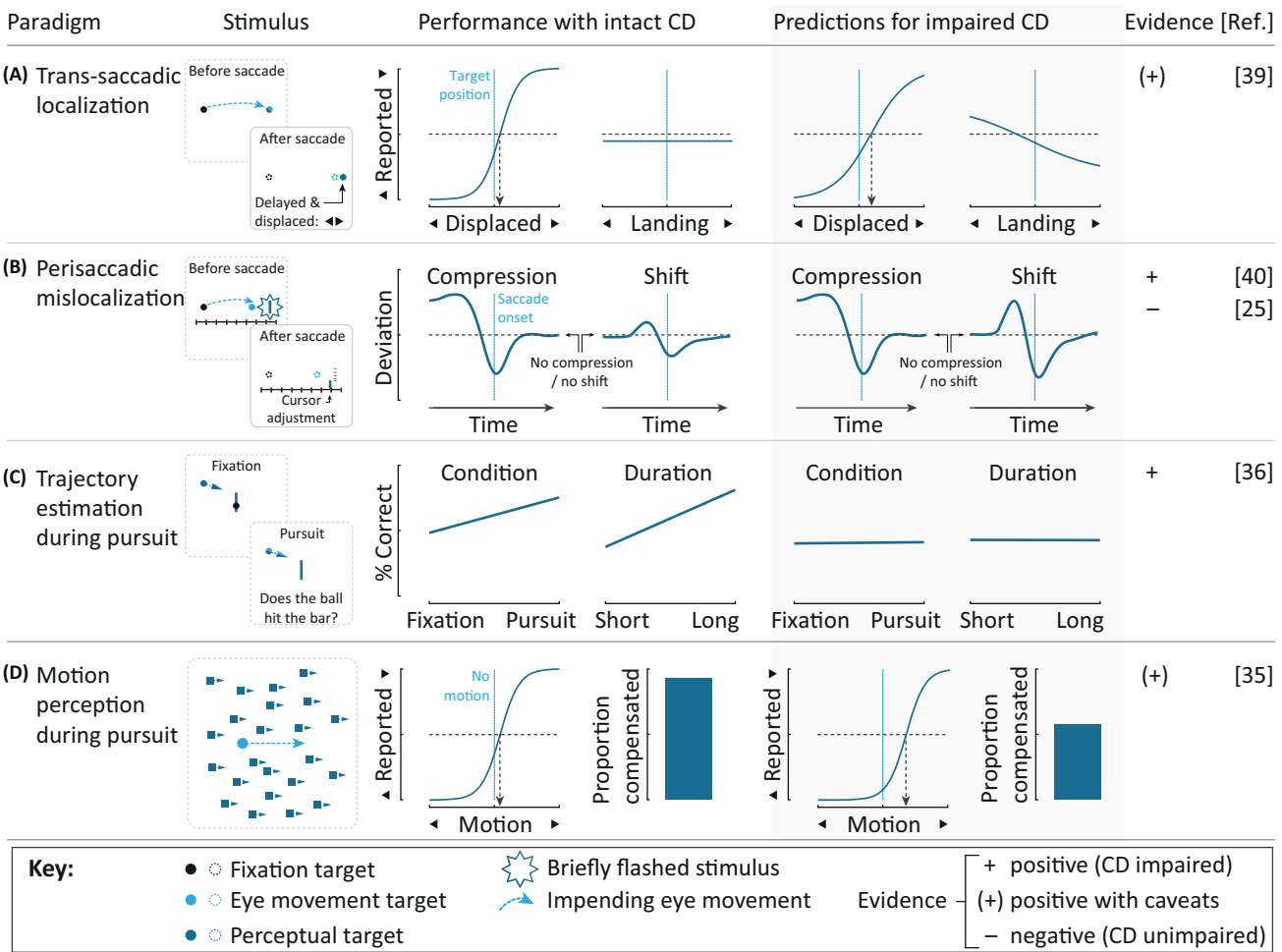


Figure 3. Oculomotor Paradigms Used to Study the Role of Corollary Discharge (CD) Signals in Perception. (A) Trans-saccadic localization. Observers judge the displacement of the saccade target, blanked upon saccade landing before reappearing displaced in one of two directions. In healthy observers, displacement reports do not depend on saccade landing site, as CD signals inform this judgment (predicted target location is the difference between the initial target distance and the amplitude of the executed saccade). If CD is disturbed, the saccadic landing site can be used as a proxy (e.g., the target is to the right of where I am looking); the displacement report thus depends on landing site. (B) Perisaccadic mislocalization. Observers perceive stimuli flashed briefly before saccades to be shifted in the direction of the saccades and closer to the saccade target. Impairment of CD is theorized to cause increased shifts. (C) Trajectory estimation. Pursuit of the ball facilitates performance in the collision judgment task, suggesting a role of CD in the task. (D) Motion perception. During pursuit, retinal motion of the background should be cancelled by CD signals.

recent work, however, has revealed that compression can be observed in the absence of a saccade, arguing instead that it is due to reduced perisaccadic visual sensitivity [43,44]. Thus, these findings of unaltered perisaccadic compression in schizophrenia do not necessarily challenge other evidence for a disturbed oculomotor CD signal.

Theories positing disturbed CD as a mechanism of psychosis predict that performance on the aforementioned oculomotor tasks should be related specifically to the psychotic symptoms of schizophrenia, the key features being hallucinations and delusions. Moreover, CD abnormalities should be associated with other disorders with prominent psychotic symptoms. Consistent with this notion, CD abnormalities have been observed in individuals with **bipolar disorder** who have a history of psychotic symptoms [45,46] and in healthy individuals with schizophrenia-like traits [47,48]. Although there is some evidence for a relationship between psychotic

symptom severity and CD alterations in schizophrenia [29,35,39], these relationships are inconsistent across studies. Indeed, many studies of CD find no such relationship, leaving open the possibility that altered CD is related to other clinical factors in schizophrenia and bipolar disorder. The lack of such symptom correlations does not necessarily preclude a relationship between CD and psychosis, however. Clinical interviews may fail to enquire about psychotic experiences most closely aligned to CD abnormalities. They are further limited by what the patient is willing to report. Indeed, implicit neurobiological measures, like oculomotor indices of CD, might be a better (or at least more reliable) index of psychopathology than interview measures. Moreover, CD disturbances could reflect symptom vulnerability, rather being a proximal mechanism of psychosis. Consistent with that notion, abnormal predictive pursuit [23,49,50] (and smooth pursuit more generally [18]) and abnormal antisaccade error corrections [28] have also been observed in asymptomatic relatives of schizophrenia patients, suggesting a genetically mediated trait. Retrospective data showing CD abnormalities in high-risk individuals who eventually develop psychosis versus those who do not [51] would be particularly illuminating in this regard, but to our knowledge, these studies have not been performed.

Although we interpret the studies presented above as supporting a disturbance in CD-based oculomotor prediction that is related to schizophrenia, and potentially psychosis broadly, we would like to highlight two potential caveats. First, the possibility of medication-related effects is relevant, given that schizophrenia is typically treated with dopamine antagonists. Yet, there are two main reasons to discount medication effects as driving impaired oculomotor CD. First, impairments have been observed in unmedicated, healthy relatives of schizophrenia patients [23,49,50] and unmedicated individuals high in schizophrenia-like traits [47,48]. Second, in the aforementioned studies, antipsychotic dose is not predictive of task performance.

Potential group differences in the integrity and utilization of sensory signals used for oculomotor processing is another consideration. Sensory signals are crucial for oculomotor behavior – at least for the initiation of eye movements. There is abundant evidence for low-level sensory abnormalities in schizophrenia [52], including in the visual domain [53]. Certainly, a failure in sensory processing of visual targets would lead to disrupted oculomotor behavior. The kind of visual processing necessary for generation of saccadic eye movements seems to be spared in schizophrenia patients as the dynamics of visually guided saccades are generally intact [54]. Schizophrenia patients have robust deficits in motion perception [55], however, which is crucial for accurate smooth pursuit eye movements. Indeed, previous studies have observed that altered pursuit initiation in schizophrenia patients was related to impaired velocity discrimination [56]. In our opinion, it is unlikely that altered visual processing can fully explain performance on the oculomotor tasks tapping CD presented earlier, though it is possible that a mismatch between the actual and predicted sensory signals in schizophrenia could arise due to a disrupted or absent prediction or due to noise in the sensory system.

Furthermore, the balance of using retinal versus CD-based extraretinal information to guide oculomotor behavior could be altered in schizophrenia. In the presence of external visual signals to guide eye movements, extraretinal signals play less of a role [57,58]. Much of the work investigating CD and predictive remapping in human and non-human primates has been performed in impoverished visual environments that would either force, or at least bias, participants to use extraretinal information. If predictive mechanisms are disrupted in schizophrenia due to abnormal CD, they might show a stronger bias toward using retinal, versus extraretinal, information to perform these tasks (see Outstanding Questions).

Finally, we would like to speculate on the relationship between altered oculomotor CD and cognitive deficits. Although not part of the formal diagnostic criteria, individuals with

schizophrenia show cognitive deficits across a range of domains [59]. Impairments in visuo-spatial working memory are particularly robust [60]. As far as we are aware, the potential contributions of CD abnormalities to cognitive dysfunction have not received any attention. However, a recent study in healthy individuals observed enhanced maintenance of information at a future saccade target in working memory, arguably via CD signals [61]. These findings suggest a possible link between CD abnormalities and working memory impairments in schizophrenia and create an avenue for investigating the relationship between CD and cognitive function more broadly.

Neural Pathways Carrying CD Signals

In their elegant neurophysiological work aimed at identifying pathways conveying CD in the monkey brain, Sommer and Wurtz [15] required a set of clear-cut criteria: (i) CD must originate from neurons involved in movement generation, occur prior to movement onset, and represent the movement's spatial and temporal dynamics; (ii) rather than traveling toward the muscles, CD must travel away from lower movement areas and thus not influence simple movement production; and (iii) disrupting a pathway involved in transmitting CD should disrupt performance on tasks requiring CD. A rich body of neurophysiology and human lesion work suggests that a pathway involving the MD satisfies these criteria and that the MD plays a crucial role in the transmission of CD associated with saccadic eye movements (Figure 1B). Specifically, inactivating MD neurons that relay signals from the superior colliculus (SC) to the frontal eye fields (FEFs) disrupts performance on the double-step task in non-human primates, causing saccade targeting errors of the second, but not first, movement [14,15]. Similar double-step-task impairments in humans with MD lesions further bolster the notion that this pathway transmits CD signals [62–64].

In addition, the CD signal transmitted from the MD may be the basis of the predictive remapping properties of FEF neurons [16] and aid in postsaccadic perceptual processing [65–67]. Neurons that show predictive remapping anticipate the consequence of the eye movement and update the landscape of neural activity in an otherwise **retinotopic** map. Such neurons are common in many oculomotor brain regions (i.e., FEF, SC, lateral intraparietal sulcus) as well as in visual cortex (reviewed in [68]). Recently, however, the story of predictive updating of neural maps has become more nuanced. By sampling a large number of locations in the visual field, it was found that receptive fields in FEF converge onto the saccade target, rather than shift in the direction of the impending saccade [69]. Follow-up recordings of presaccadic changes in the receptive field of V4 neurons indicated that predictive remapping as well as convergence onto the saccade target can occur in the same neuron, albeit at different timescales and dependent on saccade direction [70]. In sum, there is considerable evidence that predictive remapping does occur on the basis of a CD signal, presumably transmitted via the MD. There is indirect evidence that remapping may begin in FEF, from where it is disseminated across the brain [71].

In the smooth pursuit eye movement system, CD signals must convey information about eye velocity. Although CD pathways associated with pursuit have not been studied with the same rigor as in the saccade system, several potential thalamocortical pathways emerge. Neurons in the ventrolateral thalamus (VL), which project to frontal oculomotor regions, contain eye velocity information consistent with a CD signal [72]. Neurons in the cerebellar flocculus, which projects to the VL, also convey a putative CD signal that it likely receives from brainstem nuclei [73]. Thus, one potential pathway for CD associated with smooth pursuit projects from brainstem oculomotor nuclei to cortical oculomotor pursuit regions (e.g., FEF) via the cerebellum and VL. Another potential pathway involves the medial superior temporal area (MST), a region that processes visual motion and projects to cortical oculomotor regions. During smooth pursuit eye movements, a class of MST neurons continues to fire in the absence of retinal motion (i.e., when the target is momentarily blanked or stabilized on the retina), consistent with the notion

that MST neurons also carry a putative CD signal [74,75]. Moreover, MST receives projections from motion-sensitive neurons in the middle temporal area, which in turn receive the effect of a CD signal conveyed from visual neurons in the SC via the pulvinar nuclei in the thalamus [76,77]. Thus, a pathway from the SC to frontal oculomotor regions via pulvinar, middle temporal area, and MST is another candidate pathway for pursuit-related CD signals. Finally, given the overlap between the saccade and pursuit systems [78], the SC–MD–FEF pathway could also transmit CD signals necessary for pursuit. This remains to be investigated.

Possible Network Mechanisms of Disturbed Oculomotor CD in Psychosis

The relevant questions in psychosis are (i) in which subnetworks is functioning altered and (ii) how do abnormalities in functional brain networks give rise to performance deficits requiring a CD signal. The precise neurophysiological characterization of a CD pathway for saccadic eye movements, and the way in which it influences sensory neurons, allows formulation of several predictions regarding macroscopic brain network function (and dysfunction; Figure 1B):

- (i) Movement neurons in the SC could fail to generate a CD signal or the relevant movement dynamics might not be conveyed in this signal.
- (ii) Dysfunction in MD neurons could prevent an accurate CD signal from being received from the SC or appropriately conveyed to the FEF.
- (iii) FEF visual neurons could fail to remap visual responses on the basis of a CD signal.
- (iv) Remapped visual information could fail to be conveyed from FEF to other visual areas.

Although these hypotheses remain to be tested, we argue that the second one (involving the thalamus) is particularly plausible. The active motor processes putatively implicated in the sense of agency depend heavily on the cortical–subcortical interface. In primates, a dense network architecture underpins this interface, with the thalamus poised in a principal role [79]. The cortex functions under a high input regime from the thalamus [80–82], and cortical–thalamic functional transactions are highly modifiable in ascending and descending directions [83]. Thus, the thalamus may be a central neuronal unit linking psychosis with neurobiology. Indeed, thalamus dysfunction and dysconnectivity are considered fundamental for explaining typical symptoms such as **thought disorder**; these inevitably reflect a lack of appropriate integration of functional signals across cortical–thalamic networks [84]. Widespread empirical support corroborates this link, including reliable evidence of thalamic structural deficits [85], dysfunctional activation profiles during saccade tasks [86], and – of particular relevance – dysfunctional thalamocortical networks. Especially salient is evidence of dysfunctional effective connectivity of cortical–thalamic network interactions, specifically involving the MD [87], and generally reduced cortical–thalamic functional connectivity at rest [88,89].

We realize that the hypotheses outlined above and in Figure 1B are not comprehensive. We have outlined other thalamocortical pathways that can convey CD in the oculomotor system and additional, redundant pathways almost certainly exist. However, the SC–MD–FEF pathway has received the most empirical support and thus forms the most solid base on which to make predictions about dysfunction in clinical populations.

Concluding Remarks and Future Perspectives

Investigation of CD in the oculomotor system capitalizes on the translational advantages that oculomotor paradigms afford, allowing novel and exciting interpretations of patient findings in the context of rich non-human primate neurophysiology data: using this system as a framework for understanding agency dysfunction in schizophrenia can lead to great strides in our understanding of the specific mechanisms of those symptoms of the illness that have been the most challenging to explain at the level of physiology. That is, oculomotor disturbances could share a common mechanism with, and potentially contribute to, the bizarre subjective experiences in psychosis. The behavioral findings in patient populations reviewed here, along

Outstanding Questions

‘How are CD signals disturbed?’ We need to develop new paradigms or utilize existing ones to identify the nature of CD disturbances in psychosis: is CD slower, less accurate, or not generated?

‘What is the neural basis of abnormal CD in psychosis?’ If further work were to establish causal relationships between activity in the FEF, SC, and MD, we could probe whether behavioral abnormalities have their basis in reduced connectivity within this network.

‘What are the phenomenological consequences of failing to perceive ourselves as the agent of an eye movement?’ Abnormal oculomotor CD should have consequences associated with the clinical picture of psychosis. The unpredicted changes in visual input caused by a failure in saccade-related CD may cause inappropriate assignment of salience, and thereby meaning, to irrelevant aspects of the environment.

‘Does the thalamus convey CD in other sensory domains?’ The clinical relevance of disturbed oculomotor CD rides on the assumption of common networks for transmitting CD across sensorimotor domains. Given its role as a versatile multimodal relay station, the thalamus is a promising candidate that should be targeted in future studies.

‘Do schizophrenia patients use alternate sources of information to infer causality?’ Unreliable CD signals may lead patients to weigh other sources of information more strongly to establish the causes of events, potentially rendering them more prone to arrive at the wrong conclusion. In the oculomotor system, for instance, individuals with schizophrenia may rely more on visual or proprioceptive signals than healthy controls to estimate the location of gaze.

‘Is there a link between CD abnormalities and cognitive dysfunction in schizophrenia?’ Recent studies suggest a possible link between CD and working memory ability, thereby creating avenues for investigating the relationship between CD and cognitive function in schizophrenia.

with an emerging psychophysical and physiological understanding of CD signals in the primate brain, create avenues for further investigation (see Outstanding Questions). Future research should explore the full translational possibilities of this work by adapting the experimental paradigms reviewed here for use as simple tests that can be performed in clinical contexts to aid in the prediction of psychosis in at-risk individuals, assist in diagnostic decisions, and track treatment-related changes over time.

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