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# Quick Phases of Infantile Nystagmus Show the Saccadic

## Inhibition Effect

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## Abstract

**Purpose:** Infantile nystagmus (IN) is a pathological, involuntary oscillation of the eyes consisting of slow, drifting eye movements interspersed with rapid reorienting quick phases. The extent to which quick phases of IN are programmed similarly to saccadic eye movements remains unknown. We investigated whether IN quick phases exhibit 'saccadic inhibition', a phenomenon typically related to normal targeting saccades, in which the initiation of the eye movement is systematically delayed by task-irrelevant visual distractors.

**Methods:** We recorded eye position from 10 observers with early-onset idiopathic nystagmus while task-irrelevant distractor stimuli were flashed along the top and bottom of a large screen at  $\pm 10^\circ$  eccentricity. The latency distributions of quick phases were measured with respect to these distractor flashes. Two additional participants, one with possible albinism and one with fusion maldevelopment nystagmus syndrome, were also tested.

**Results:** All observers showed that a distractor flash delayed the execution of quick phases that would otherwise have occurred around 100 ms later, exactly as in the standard saccadic inhibition effect. The delay did not appear to differ between the two main nystagmus types under investigation (idiopathic IN with unidirectional and bidirectional jerk).

**Conclusions:** The presence of the saccadic inhibition effect in IN quick phases is consistent with the idea that quick phases and saccades share a common programming pathway. This could allow quick phases to take on flexible, goal-directed behaviour, at odds with the view that IN quick phases are stereotyped, involuntary eye movements.

## Introduction

Infantile nystagmus (IN) describes a syndrome of involuntary, pathological oscillations of the eyes that are almost invariably conjugate, symmetrical and horizontal.<sup>1</sup> IN is estimated to affect around 14 in every 10,000 people<sup>2</sup> and, although not usually present at birth, is commonly established by about three months of age.<sup>2</sup> <sup>3</sup> Twelve types of IN waveform have been identified and are typically split into two groups, termed 'jerk' and 'pendular'.<sup>4</sup> Jerk IN is characterised by slow accelerating drifts away from fixation that are interspersed with resetting quick phase 'jumps' that bring the fovea back toward the object of regard. Pendular waveforms are dominated by slow, smooth eye movements, both toward and away from fixation. Although the waveforms associated with jerk and pendular nystagmus appear very different, these pathological eye movements are thought to share a common underlying cause. Jerk waveforms often emerge from pendular nystagmus during infancy,<sup>5-7</sup> and adults with jerk nystagmus can show pendular oscillations during periods of inattention.<sup>1, 8, 9</sup> Moreover, prolonged eye movement recordings from any one individual often reveal the expression of more than one waveform type.<sup>1</sup>

How and why IN arises is subject to continuing debate (for a recent review see Gottlob and Proudlock<sup>10</sup>). IN presents alongside a wide range of afferent visual system pathologies, including (but not limited to) albinism, congenital cataracts, optic nerve hypoplasia and retinal diseases such as achromatopsia.<sup>2, 3, 11, 12</sup> The numerous afferent visual system pathologies associated with IN make it difficult to establish aetiology, and furthermore, a sizable proportion of IN cases do not appear to be associated with any ocular pathology whatsoever (these are referred to as 'idiopathic' or 'isolated' IN).<sup>2, 10, 13</sup> The underlying cause of IN has variously been

attributed to abnormalities in neural mechanisms responsible for gaze holding,<sup>1, 8, 14</sup> malfunction of smooth pursuit feedback,<sup>8, 15-17</sup> malfunction of the optokinetic response,<sup>18-21</sup> and malfunction of saccadic termination.<sup>22-25</sup> More recently, Harris and Berry<sup>6, 11, 26</sup> proposed that IN results from an intact oculomotor system, but one which has settled on an abnormal viewing strategy. This abnormal strategy may have originally been an adaptive oculomotor response to improve low spatial-frequency information during early development; however, the strategy becomes maladaptive following full development of visual acuity.<sup>6, 11, 26, 27</sup>

The pathological part of the eye movement in jerk IN is usually considered to be the slow phase.<sup>28</sup> It is the slow phase that takes the eye away from the desired gaze location, while quick phases are executed to halt the runaway slow phase and re-align the fovea with the visual target.<sup>15, 16, 29</sup> The quick phases of IN therefore appear to be similar to saccadic eye movements: they show the same relationship between amplitude and peak velocity (the main sequence)<sup>30</sup> and exhibit the same peak intersaccadic interval.<sup>31</sup> Moreover, both quick phases and saccades show dynamic overshoots.<sup>32</sup> Yet despite these similarities, quick phases are normally considered to be involuntary<sup>33</sup> and made without the individual being aware of them<sup>6</sup>. Quick phases are therefore not considered to be subject to top-down influences typically associated with saccades, such as the superior colliculus (SC) or the many cortical centres involved in eye movement control.<sup>34-37</sup>

This view is somewhat contrary to the evidence that quick phases interact with saccades, suggesting (albeit indirectly) that the former benefit from some degree of central processing. For example, Worfolk and Abadi<sup>33</sup> measured saccadic accuracy in participants with IN, and found that visual targets displaced in the same direction as ongoing quick phases resulted in a saccade that overshoot the target,

while target displacements in the opposite direction resulted in a saccade that undershot the target. They suggested that the desired end-points of quick phases and voluntary saccades interact in a way analogous to the 'global effect'<sup>38, 39</sup> commonly seen in saccades, such that the landing point of the subsequent eye movement lies somewhere in between the competing desired locations signalled in the saccadic planning maps of areas like SC. Additionally, Wang and Dell'Osso<sup>40</sup> found that saccade latencies are particularly long if a saccade target is presented around the time of a quick phase, suggesting that quick phase programming may delay concurrent saccadic planning. More crucially, both studies showed that quick phases themselves can be modified or suppressed when targeting saccades are called for, a result in keeping with the suppression found during reading<sup>41</sup>. In the present study, we therefore sought a more direct test of the central programming of quick phases, by investigating whether they show the 'saccadic inhibition effect'.

The saccadic inhibition effect is a remarkably robust phenomenon whereby the onset of an irrelevant distractor stimulus delays the execution of saccades that would otherwise have occurred around 100 ms later. This creates a characteristic dip and rebound in the latency distribution when plotted with respect to distractor stimulus onset.<sup>42-47</sup> The saccadic inhibition effect is thought to occur because the onset of the distractor stimulus automatically drives activity in the oculomotor system, delaying the rise-to-threshold of saccade-related activity through mutual inhibition within saccade planning maps, such as those found in the SC.<sup>44, 48-50</sup> Recent evidence has shown that the fast-phases of optokinetic nystagmus, also considered largely involuntary, exhibit the saccadic inhibition effect<sup>51</sup>. We therefore asked whether IN quick phases behave in a similar fashion. Specifically, if quick

phases share some of the same processing as saccades, we predicted they too should exhibit the saccadic inhibition effect.

## Methods

### Participants

Twelve observers participated in the study, all of whom were recruited from the Research Unit for Nystagmus at the School of Optometry and Vision Sciences, Cardiff University. Table 1 summarises the participant information. The first 10 participants were diagnosed with idiopathic IN: eight had a unidirectional jerk waveform, and two displayed bidirectional jerk. None presented with pendular nystagmus. The eleventh participant presented with iris transillumination and a small foveal pit as indicated from an optical coherence tomogram and so was diagnosed with possible albinism. The twelfth participant was diagnosed with fusion maldevelopment nystagmus syndrome (FMNS), formerly known as ‘latent nystagmus’. FMNS is manifest during occlusion of one eye and is characterised by decelerating slow phases (as opposed to the acceleration seen in IN).<sup>28</sup> These fundamental differences mean that FMNS is not considered a sub-type of IN, despite the fact that both arise in infancy.<sup>28</sup> Of course, with only one participant diagnosed with FMNS and one with possible albinism, any conclusions drawn from this study about the nature of saccadic inhibition effect in these types of observer are **illustrative** at best.

All observers underwent a clinical examination by an optometrist, including slit-lamp examination, ophthalmoscopy and optical coherence tomography. During the experiment, observers used their own spectacle correction, if needed.

All procedures were conducted in accordance with the Declaration of Helsinki, and this experiment was approved by the ethics committee of the School of Psychology, Cardiff University. All participants gave informed consent prior to undertaking this experiment, and were debriefed afterward.

Table 1: Details of participants

<b>Participant</b>	<b>Sex</b>	<b>Age</b>	<b>Waveform group</b>	<b>Pathology</b>	<b>Eye alignment</b>
DB	M	53	Unidirectional jerk	Idiopathic	Orthotropia
GS	M	28	Unidirectional jerk	Idiopathic	Orthotropia
GT	M	59	Unidirectional jerk	Idiopathic	12 <sup>Δ</sup> alt. esotropia
JC	M	69	Unidirectional jerk	Idiopathic	Orthotropia
JC2	F	54	Unidirectional jerk	Idiopathic	Orthotropia
JS	M	55	Unidirectional jerk	Idiopathic	Orthotropia
JT	M	24	Unidirectional jerk	Idiopathic	Orthotropia
LF	F	19	Unidirectional jerk	Idiopathic	Orthotropia
NB	M	44	Bidirectional jerk	Idiopathic	Orthotropia
RW	F	83	Bidirectional jerk	Idiopathic	Orthotropia
<i>RC</i>	<i>F</i>	<i>22</i>	<i>Bidirectional jerk</i>	<i>Possible albinism</i>	<i>15<sup>Δ</sup> right exotropia</i>
<i>KL</i>	<i>F</i>	<i>60</i>	<i>Manifest FMNS</i>	<i>FMNS</i>	<i>5<sup>Δ</sup> left exo / 2<sup>Δ</sup> hypertropia</i>



### Materials

Eye position was recorded using an EyeLink 2000 eye tracker (SR Research, Ottawa, Canada) mounted on a chin and forehead rest. The eye tracker recorded eye movements at a rate of 1000 Hz using standard video-based technology. Note that although participants viewed the stimuli binocularly, the eye tracker recordings were monocular. As the oscillations of nystagmus are conjugate, however, any change in fixation from one eye to the other would not affect the measured timings of the eye movements upon which the current paradigm relies.

Participants were seated in darkness with the chin and forehead supported. The viewing distance was 140 cm from the centre of a large screen (2.08×1.56 m, 1024×768 pixels). The screen had an embedded Fresnel lens, the purpose of which was to collimate light more evenly throughout the display. Stimuli were rendered using OpenGL software running on a Radeon 9800 Pro graphics card and rear projected using a Sony Multiscan projector (VPH 1272QM) running at a refresh rate of 72 Hz. Gamma correction was achieved using standard techniques. Only the central 'green' cathode ray tube of the projector was used.

### Stimuli and Procedure

During the experiment, participants were asked to maintain gaze as best as possible upon a single target comprising a green dot with radius of  $0.5^\circ$  and brightness of  $1.24 \text{ cd/m}^2$ . Due to the presence of a 'null zone' of gaze, some individuals with IN can find it uncomfortable to maintain gaze straight ahead<sup>1</sup>. For this reason, before the experiment began, the target's 'central' location was shifted so that the

participant could comfortably direct their gaze upon the target while keeping their head in the appropriate orientation for the eye tracker.

The experiment consisted of 40 trials, each of which lasted for 30 s. During this time, the participant maintained gaze upon the target while two distractor bars above and below were flashed intermittently for 30 ms (see Figure 1 for schematic). Each bar subtended  $73.2^\circ$  by  $19.12^\circ$  and had a brightness of  $1.24 \text{ cd/m}^2$ . The inner horizontal edges of the bars were  $\pm 10^\circ$  from central fixation. The time between each distractor flash was randomly selected to occur between 750 and 1250 ms. There were 30 flashes per trial, with a potential for 1200 distractor-to-quick-phase intervals per participant. At the end of each trial, a blank screen was presented, and the participant was given the opportunity to rest. The participant initiated the next trial with a button press.

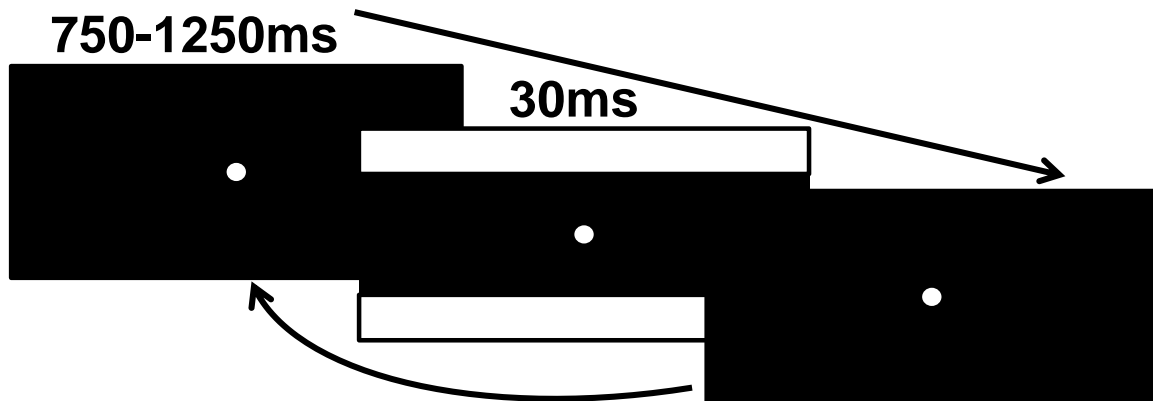


Figure 1: Schematic of stimulus presentation (not to scale). Gaze was directed toward a single fixation target, and every 750-1250 ms, two large distractor stimuli were flashed briefly for a duration of 30 ms (see centre panel).

### Data Analysis

One advantage of this paradigm is that it does not need the eye tracker to be spatially calibrated, which is always difficult in IN because of the persistent eye movement. This is because the onset of the quick phase can be determined using the *relative* change in eye position – absolute position is not required. For this reason, we express eye position in arbitrary units throughout. Quick phases were detected using a relative velocity criterion that was manually adjusted until the software's ability to locate quick phases corresponded to those determined by visual inspection of the waveform. The actual quick phase onset was defined as the point at which velocity first rose above a particular value, the latter also determined by inspection. The accuracy of quick phase detection was checked visually for every distractor stimulus onset. This then allowed measurement of the latency between each distractor flash and the subsequent quick phase. We note in passing that, since our paradigm avoids the need for specialist calibration algorithms, it can more easily be adopted by other researchers in the field.

It is standard practice in the saccadic inhibition paradigm to create a baseline distribution of saccade latencies where no distractor is presented<sup>44</sup>. In the current experiment, however, the quick phase is self-initiated rather than triggered by presentation of a visual target, and so there is no external event upon which to time-lock quick phase latencies. To create a baseline 'no-distractor' distribution, we therefore followed the simulation procedure described by Harrison, Freeman and Sumner<sup>51</sup>. An array of random time points was created throughout the dataset, each acting as the start of a 'phantom' distractor that could be used to simulate the time locking of the next quick phase. The time points were selected randomly from the range 750 to 1250 ms (the same timing as the distractors), with the next quick phase

following each chosen time point used to create the baseline distribution. This procedure was then repeated 100 times (with different random time points each time) to create a very large dataset. If any of the selected quick phases was the first to follow an actual distractor flash it was removed from this dataset. This left baseline 'no-distractor' distributions of between 68,000 and 107,000 data points per participant (depending upon quick phase frequency).

Following Bompas and Sumner<sup>48</sup>, latencies in both the distractor and no-distractor conditions were taken with a bin size equal to the temporal resolution of the eye tracker (1ms in our case) and then smoothed using a Gaussian filter (SD = 1ms, with the filter kernel rendered over a 20 ms wide window). A distractor ratio<sup>47, 48</sup> was then calculated as  $\frac{\text{baseline-distractor distribution}}{\text{baseline}}$ , and the time at which the ratio first rose above 2% was used as the dip-onset point.<sup>42</sup>

## Results

Examples of the eye movements produced by individuals with the two different idiopathic nystagmus waveform types encountered in this experiment are shown in Figure 2A-B. Eye position is expressed in arbitrary units, given that, as discussed above, absolute position calibration is not necessary to determine subsequent latency distributions.

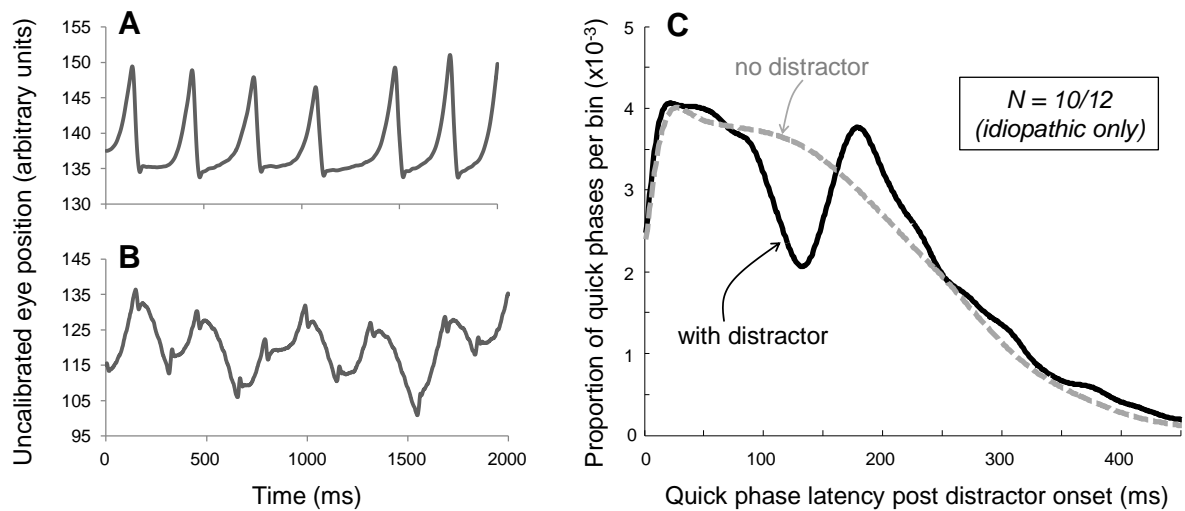


Figure 2: Example waveforms from: (A) unidirectional jerk nystagmus (Participant LF) – note the increasing acceleration of the slow phase; (B) bidirectional jerk nystagmus (Participant NB) – note the braking and foveating quick phases at each peak of the slow, pendular waveform; (C) Mean latency distributions for the ‘with distractor’ condition (solid line) and simulated ‘no distractor’ condition (dashed line), averaged over the 10 participants with idiopathic IN. The latencies are time-locked to the onset of the distractor stimulus.

A summary of the impact of distractor stimuli on latency distributions of quick phases is shown in Figure 2C. The solid line plots the mean distribution for the ‘with distractor’, averaged bin by bin across all 10 participants with idiopathic IN. For comparison, the simulated ‘no-distractor’ baseline distribution is shown as a grey

dashed line. The mean ‘with distractor’ distribution shows evidence of a dip between approximately 60-150ms, followed by a later rebound between approximately 160-240ms where the proportion of quick phases in the distractor condition rises above the no-distractor distribution. The mean ‘with distractor’ distribution therefore suggests that the quick phases of IN exhibit a typical saccadic inhibition effect.

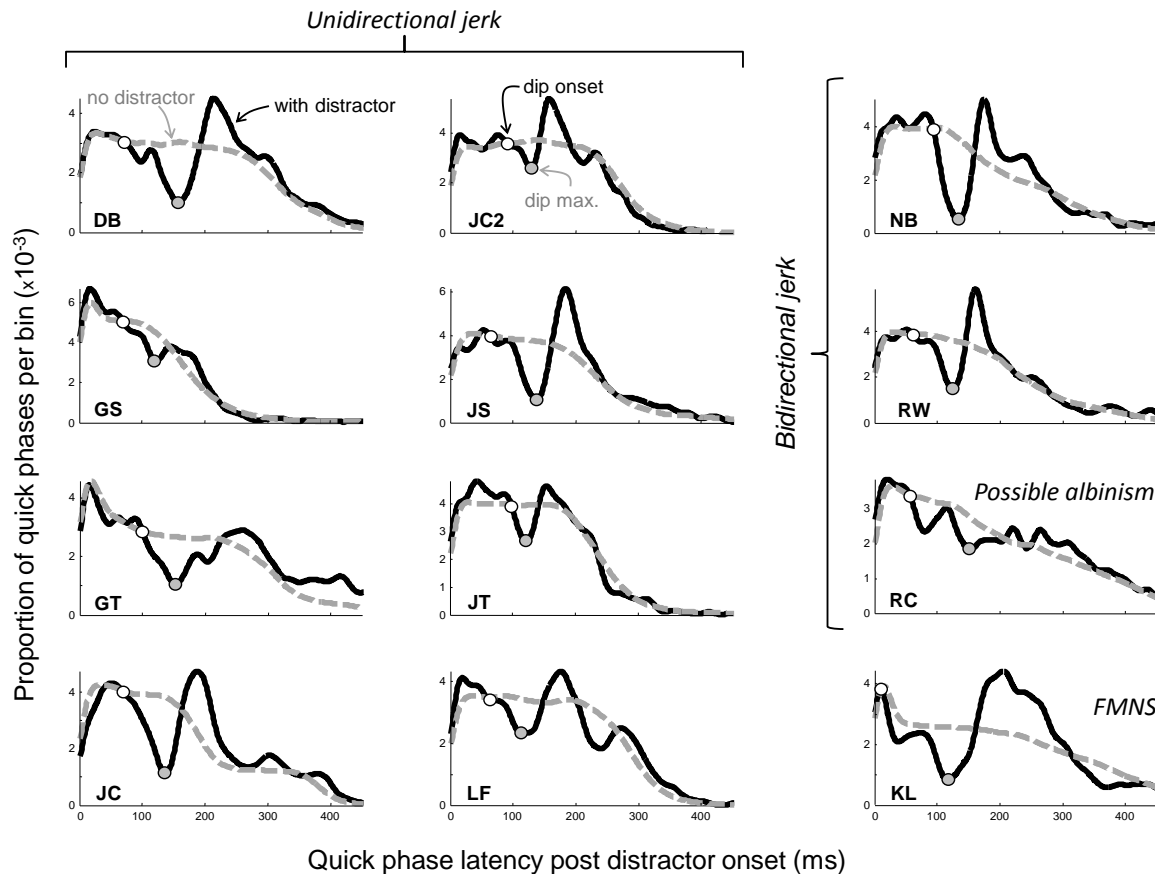


Figure 3: Individual data showing distributions of quick phase latencies relative to distractor stimulus onset (solid line) and the simulated 'no-distractor' condition (dashed line). Blank circles denote detected dip onsets; filled grey circles denote detected dip maxima. We caution against drawing strong conclusions on the basis of the single individuals with possible albinism (participant RC) and FMNS (participant KL). They have been included for illustrative purposes only.

This conclusion holds up to closer scrutiny across all the participants tested. The individual distributions shown in Figure 3 reveal that all 12 participants exhibited a saccadic inhibition effect. Moreover, the mean dip onset times were consistent with

those previously published in the saccadic inhibition literature.<sup>44, 48, 49</sup> For the eight idiopaths with unidirectional jerk, the mean dip onset was 79 ms (SD = 16 ms); for the two idiopaths with bidirectional jerk, the mean was 76 ms (SD = 26 ms). The close similarity between these means also suggests that the saccadic inhibition effect is independent of the type of idiopathic IN present, although it is difficult to draw a definitive conclusion given the low numbers of participants in the study. Nevertheless, other characteristics of the observed dips were also broadly similar across these two groups. The mean time at which the dip maximum occurred was 134 ms (SD = 16 ms) for idiopaths with unidirectional jerk, compared to 142 ms (SD = 11 ms) for the idiopaths with bidirectional jerk. Moreover, the mean amplitude of the dips were 49% (SD = 19%) and 59% (SD = 36%), respectively.

## Discussion

We have shown that the saccadic inhibition effect reliably occurs for the quick phases of IN. This finding is consistent with the idea that quick phases and saccades are generated by similar, if not identical, sensorimotor mechanisms. If correct, the similarities between these two types of ballistic eye movement would therefore appear to extend beyond the basic motor machinery itself.

### *Putative site of visual-oculomotor interaction*

The saccadic inhibition effect is likely to arise from activity in the SC because the onset of inhibition is highly consistent with the SC's known conduction and response times<sup>44</sup>. Moreover, sub-threshold microstimulation of the SC affects saccades in the same way as distractor stimuli do<sup>52</sup>, and saccadic inhibition is an emergent property

of models of the SC<sup>48, 53</sup>. However, we cannot rule out the possibility that the effects reported here may stem from other brain loci. Sudden visual transients have been shown to affect the activity in omnipause neurons as well as those in SC.<sup>54-56</sup> Conversely, models of SC also exhibit properties associated with the frontal eye fields.<sup>48</sup> The saccadic inhibition effect could therefore arise from multiple sites.

### *The relationship between IN quick phases and saccades*

The onset of inhibition in the quick phases of IN is highly consistent with the previously published onset times using saccades in normal observers.<sup>38, 42, 43</sup> We suggest, therefore, that this provides further evidence that the quick phases of IN are fundamentally saccadic in nature. This idea is consistent with the observation that quick phases and saccades have similar main sequences and intersaccadic intervals,<sup>30, 31</sup> and that saccadic accuracy and latency can be altered by quick phase activity.<sup>33, 57</sup> Moreover, it lends support to those who claim that the oculomotor system in people with IN is functionally intact but uses a different viewing strategy.<sup>11, 40</sup> However, as highlighted in the Introduction, there are a number of other possible explanations of IN, many of which are not directly addressed by our paradigm and so cannot be ruled out by our results.

We did not observe any obvious difference between the inhibition effect in unidirectional jerk and bidirectional jerk nystagmus. Whilst a difference might have been observed were we able to collect data on more individuals, we have little reason to suppose that such a difference would occur. This is because both types of waveform are considered to be manifestations of the same nystagmus phenotype.<sup>5, 6</sup> That said, for bidirectional jerk waveforms, there is a distinction between a quick



phase that occurs at the peak farthest from desired gaze location (a 'braking quick phase', serving to halt the runaway slow phase and initiate a slow phase back toward target location) and a quick phase that occurs at the target location (a 'foveating quick phase', serving to align the fovea with desired gaze location).<sup>29</sup> Unfortunately, without eye tracker calibration, we cannot differentiate between braking and foveating quick phases. Nevertheless, we found no discernable difference between the inhibition effect in those with unidirectional and bidirectional jerk nystagmus, which suggests that braking and the foveating quick phases are affected in the same way by the distractor stimulus. This agrees with the finding that voluntary saccade latency is prolonged equally by target steps around the time of a foveating or a braking quick phase.<sup>40</sup> On this basis, despite the different requirements of these two fast eye movements<sup>29</sup>, we would argue that they are generated by the same neural mechanisms.

We were able to test our paradigm on only one individual with FMNS and one with possible albinism. With only single observers in each category, we must be cautious about the conclusions that can be drawn over detailed differences and/or similarities with idiopathic IN. Nevertheless, both these observers exhibited a clear saccadic inhibition effect. At the very least, we can say that the saccadic inhibition effect is present in all the quick phases of nystagmus that were analysed in our study.

### *The role of saccade planning in quick phase generation*

Our results clearly show that the quick phases of IN can be modified by external visual information. Therefore, despite the apparently involuntary nature of quick

phases, there appears little fundamental distinction between this type of ballistic eye movement and saccades. A similar conclusion has recently been drawn for the relation between the fast phases of optokinetic nystagmus and saccades, based in part on the finding that fast phases also exhibit the saccadic inhibition effect<sup>51</sup>. We therefore expect to see other saccade-like behaviour associated with quick phases. For instance, it has been reported that, when visual target displacements are small, observers with IN are likely to acquire them with an ordinary quick phase, rather than making a distinct saccade.<sup>33, 58</sup> This implies that the quick phases of IN can take on targeting properties, which would require some form of top-down influence to modify the end-point of the eye movement. Conversely, when executing targeting saccades<sup>33, 40</sup>, as well as reading<sup>41</sup>, individuals with IN are able to modify or suppress their quick phases to help with the task at hand.

Some top-down control is also consistent with the observation that quick-phase frequency depends upon the attempt to maintain fixation. For example, a conscious effort to fixate a target is reported to result in more frequent quick phases, and periods of inattention can induce slow pendular oscillations.<sup>1, 8</sup> Moreover, changes in frequency can also be related to levels of visual demand, arousal and/or mental effort. Nystagmus intensity (frequency × amplitude = average velocity of the eye movements) therefore increases if a participant performs mental arithmetic with their eyes closed or is given stressful electric stimulation.<sup>1, 59</sup> Interestingly, nystagmus intensity reduces, and the waveform itself appears to be modulated to aid visual functioning when viewing high spatial frequency stimuli in a low-stress situation.<sup>60</sup> All of these lines of evidence would suggest that the IN waveform is in some sense adaptive to visual demand, as well as being responsive to the overall level of arousal. We believe that connections with higher-level oculomotor areas

could be the pathway that enables quick phases to subserve such flexible, goal-related behaviour. Assuming a sharp distinction between voluntary and automatic eye movements may therefore be less useful than assuming a graded influence of top-down goal-directed behaviour on more automatic movements such as the quick phases of IN.

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