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Cervical dystonia: a disorder of the midbrain network for covert attentional orienting

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INTRODUCTION

Cervical dystonia, characterized by sustained or intermittent neck muscle contractions causing abnormal head movements, is the most common form of adult-onset idiopathic isolated focal dystonia (AOIFD) and may be sporadic or familial (1). The pathogenesis of cervical dystonia is unknown (2). In patients with cervical dystonia, a number of neurophysiological and neuroimaging abnormalities have been described as endophenotypes implying a relationship to causal mechanisms [reviewed in Ref. (3)]. We have argued that many of these abnormalities are secondary endophenotypes resulting from disease manifestation; only mediational endophenotypes, including abnormal temporal discrimination, found in unaffected first-degree relatives as well as patients, are relevant to understanding disease pathogenesis (4, 5) (Table 1). The features of a mediational endophenotype are (a) it is an expression of a genetic mutation, necessarily present prior to disease onset, (b) it reflects disease susceptibility and is not altered by disease expression or severity, and (c) it is more penetrant than the phenotype (6). The attributes of abnormal temporal discrimination which indicate that it is a mediational endophenotype of cervical dystonia are listed in Table 1.

Mediational endophenotypes may elucidate mechanisms of disease pathogenesis not obvious from the phenotype. Shared pathological mechanisms for both disordered temporal discrimination and cervical dystonia have become evident over the past 10 years from highly sophisticated piecemeal investigations in diverse disciplines including primate and sub-primate neurophysiology, anatomy, chemistry, psychology, and clinical research. Using this evidence, we propose a unified theoretical model to explain the etiopathogenesis of cervical dystonia.

HYPOTHESIS

We postulate that cervical dystonia is a disorder of a midbrain network for covert attentional orienting involving both the sensory and motor laminae of the superior colliculus. The mediational

Abbreviations: AOIFD, adult-onset idiopathic isolated focal dystonia; DLSC, intermediate and deep laminae of the superior colliculus; SLSC, superficial laminae of the superior colliculus; SNpr, substantia nigra pars reticulata; TDT, temporal discrimination threshold; WFV, wide field vertical.
endophenotype, abnormal temporal discrimination and the phenotype, cervical dystonia, are caused by defective inhibition of sensory and motor neurons in the superior colliculus. This disinhibition is due to the effects of reduced gamma-aminobutyric acid (GABA) activity, both from the substantia nigra pars reticulata (SNpr) and GABAergic interneurons within the superior colliculus. Abnormal temporal discrimination, a subclinical marker of this disinhibition, results from prolonged duration firing of visual sensory neurons in the superficial layers of the superior colliculus (SLSC). The abnormal involuntary movement characteristic of cervical dystonia results from subsequent secondary disinhibition of cephalomotor neurons in the intermediate and deep layers of the superior colliculus (DLSC). A summary of the arguments deployed in support of this hypothesis is outlined in Table 2.

MIDBRAIN NETWORK FOR COVERT ATTENTIONAL ORIENTING

Attentional networks in the brain can be divided into: (i) an overt (top-down) attentional network utilizing volitional eye movements to orient the visual system and (ii) a covert (bottom-up) network, which shifts attention to locations by head movements with or without saccade initiation (13). The midbrain covert attentional network captures change in the environment and alerts the individual to a salient stimulus, which requires inspection and action that may be important for survival. A significant node in this network is the superior colliculus, a complex sensorimotor network dedicated to detecting and responding to salient changes in the environment.

Table 2 | An outline summary of some of the more important experimental evidence from clinical and animal studies supporting the hypothesis that both abnormal temporal discrimination and adult-onset isolated focal dystonia are due to a disorder of reflex covert orienting caused by defective GABAergic inhibition in the superior colliculus.

Hypothesis: pathologically disinhibited midbrain network for covert orienting and deficient GABAergic activity causes

(a) Subclinically, abnormal temporal discrimination due to disordered visual processing in the SLSC
(b) Clinically, cervical dystonia due to disinhibited prolonged burst activity of cephalomotor neurons in the DLSC

Key observations in support of the hypothesis

**Sensory aspects**

1. The midbrain network for covert attentional orienting is a primitive, highly conserved system for detecting salient environmental change, inspecting the change, and responding rapidly and appropriately.

2. Wide field visual sensory neurons in the SLSC, via the retinotectal pathway, detect environmental visual change and respond by transient discharges to the pre-motor neurons for saccade generation and head turning.

3. Focal inactivation of the SLSC causes loss of covert visual attention in the visual field represented by the inactivated part of the SLSC.

4. Inhibitory GABAergic activity (within the superior colliculus and from the SNpr) limits the duration of the transient response in visual sensory neurons in the SLSC.

5. A moving or sudden luminant visual stimulus elicits a time-locked electromyographic response in cervical muscles involved in ipsilateral head turning.

**Motor aspects**

1. Movement is initiated by the striatum through release from the tonic inhibition exerted by the SNpr. A core neurophysiological feature of dystonia is reduced inhibition at all levels of the CNS; the most probable cause is defective GABAergic inhibition.

2. The oculomotor and cephalomotor pre-motor neurons of the DLSC for saccade generation and head turning are tonically inhibited by the SNpr. Release from that inhibition allows prolonged burst discharges of premotor neurons.

3. Oculomotor premotor neurons are gated by omnipause neurons; the cephalomotor premotor neurons are not gated.

4. Stimulation of cephalomotor neurons in the DLSC causes ipsilateral head turning in monkeys via the tectospinal and recticulospinal fiber tracts terminating in the cervical cord.

5. A unilateral lesion of the SNpr in macaques causes a movement disorder resembling cervical dystonia. A further lesion in the superior colliculus abolishes/attenuates the movement disorder.

This argument is expanded and fully referenced in the text. AOIFD, adult-onset isolated focal dystonia; DLSC, intermediate and deep laminae of the superior colliculus; SLSC, superficial laminae of the superior colliculus; SNpr, substantia nigra pars reticulata; TDT, temporal discrimination threshold.
A significant intrinsic population of GABAergic inter-neurons muscles. A required appropriate motor output for immediate inspection detect that change, and integrate the sensory information into receive multisensory inputs relating to environmental change, tile and auditory inputs (15). Thus, both the SLSC and the DLSC deeper laminae of the superior colliculus receive other salient tac- control of attention (28–30).

directed to the visual field corresponding to the stimulation site, ing an odd-ball salient stimulus in the inactivated visual field and visual sensory area in the SLSC prevents macaques from detect- (24, 25).

MOTOR OUTPUT OF SUPERIOR COLLICULUS
While the classical concept of the motor function of the superior colliculus is that of a saccade generator, recent studies in macaques have highlighted other motor functions.

SACCADE GENERATION (OCULOMOTOR PREMOTOR NEURONS)
Saccades are driven by brief, high-frequency, bursts from the DLSC to the brain stem burst generator (39). This oculomotor drive is potently inhibited by the pontine omnipause neurons. These tonically prevent the premature execution of eye movements until the DLSC output reaches a threshold, which is usually associated with the high-frequency burst. Low-frequency DLSC activity does not influence eye movement because of this gating by the omnipause neurons (40). Visually guided saccades have latencies of 150–350 ms; both humans and monkeys can generate express sac- cades with latencies of 70–100 ms in monkeys and 80–120 ms in humans (41).

HEAD-TURN GENERATION (CEPHALOMOTOR PREMOTOR NEURONS)
Initial studies in cats demonstrated that stimulation of the DLSC elicited early head movements without saccades (42) (Figure 1).
In macaques, a number of experiments in the last 15 years have revealed that the DLSC contains premotor neurons solely concerned with head-turn generation; this motor pathway has not been examined in human. In macaques, the sudden presentation of a bright target in the temporal visual field stimulates a discharge of DLSC premotor neurons and a time-locked burst of activity in ipsilateral neck muscles with an extremely short latency (55–95 ms after the visual stimulus), regardless of the ensuing saccadic reaction time (43, 44) (Figure 1). This has been termed the "visual grasp reflex" (44). When a gaze shift (head plus eye movement) does follow, the neck muscle electromyographic response increases significantly prior to the higher velocity head movement associated with the gaze shift reflecting a correlation with movement preparation (45, 46). Low-frequency stimulation of DLSC neurons generates head turns without saccades in macaques and, in one study, 26% of DLSC neurons sampled were head-only neurons (42, 43, 47–50). In contradistinction to the oculomotor pathway, an absent or significantly weaker gating mechanism on the head pathway permits the generation of head-only movements that can precede gaze shifts (48, 51–53). Monkeys trained to make head-only movements to reward (without gaze shifts) showed DLSC neuronal bursts 20 ms before neck EMG activity (46); the classical DLSC neurons involved in gaze shift (head and eye movement) are not active in such head-only movements (54). In the sub-human primate, the representation of the position of head on body in the superior colliculus is used to compute oculomotor movement in saccade execution (55).

UPPER LIMB MOTOR CONTROL FROM THE SUPERIOR COLLICULUS

The primate superior colliculus also contains neurons which, when stimulated, produce arm movements independent of gaze shift (57–59); these neurons affect the shoulder and proximal arm muscles (57) and even hand muscles (60). In humans performing a reaching task with one arm following the sudden appearance of a visual target stimulus, there was a time-locked response in shoulder muscles at a latency of <100 ms indicating a rapid neural pathway linking visual input to arm movement; this seemed most effective during reflexive movement tasks (61). The DLSC is the primary source of this short latency response.

OTHER SUPERIOR COLLICULUS OUTPUT TARGETS

These targets include substantia nigra pars compacta, SNpr, and the intralaminar nucleus of the thalamus (14, 62).
ANATOMY OF THE PATHWAYS FOR THE HEAD-TURN RESPONSE TO SUPERIOR COLLICULUS STIMULATION

In macaques, anatomical studies have shown that projections to downstream oculomotor and neck muscle structures originate in separate laminae of the stratum griseum intermediale in the DLSC (63, 64) (Figure 2). The tectospinal tract is a very conserved structure present in all mammals, although it is better developed in predatory than in less predatory species (65, 66). It originates in the DLSC and terminates almost exclusively on inter-neurons in the upper cervical cord whose motor neurons innervate neck muscles, and in the lower cervical enlargement innervating the forearm and hand muscles (65, 67, 68). Another important tectospinal target is the propriospinal neurons in the C3–C4 segments of the cervical cord, which govern target reaching of the forelimb (69).

The tecto-reticulospinal tract also originates in the DLSC of the SC, involves the tegmental and pontine reticular formation and also ends in the upper cervical spinal cord (67, 68, 70–73) contacting, at least in part, the motor neurons of head extensor muscles. The cells of origin of the tectospinal and the tecto-reticulospinal tracts overlap to some degree in the DLSC (73). Electrical stimulation of the DLSC and the dorsal tegmentum in the cat activates reticulospinal neurons (74) that in turn activate motor neurons of the flexor and extensor muscles of the hind and forelimb (75). In the macaque, tecto-reticulospinal pathways to the neck and hand muscles have been demonstrated (76); neck muscle EMG activity following a visual stimulus is conveyed by the tecto-reticulospinal pathways (77). In cats, this pathway displays bursts of activity time-locked to visual target presentation (78). Similar burst discharges in response to visual stimuli have been found in tecto-reticular neurons in rats (79).

VISUAL RESPONSE IN THE SUPERIOR COLLICULUS

Among others, the Okazaki laboratory of Tadashi Isa has been extremely active in examining the microcircuitry of the superior colliculus (Figure 3). The predominant cell type in the superficial layer of the superior colliculus is the wide field vertical (WFV) cell, mainly in the stratum opticum of the SLSC; these cells have characteristic dendritic trees and are luminance and motion sensitive (Figure 3). In response to a visual stimulus, most of the neurons in the SLSC exhibit transient "ON" responses within 50 ms of the stimulus onset (80). With a persistent visual stimulus, most of these cells enter a pause phase and then only discharge again when the visual stimulus is switched off. This sequence "ON–PAUSE–OFF" (Figure 3) in the WFV neurons is characteristic of the response in the superior colliculus to the switching on and off of the visual stimulus or the response to movement. This is the mechanism by which the superior colliculus acts as a detector of salient stimuli (Figure 3).

GABAergic INHIBITION IN THE SUPERIOR COLLICULUS AND NORMAL TEMPORAL DISCRIMINATION

Application of a GABA_A antagonist to an electrode recording SLSC neuronal responses to optic fiber inputs in mice prolongs the “ON” burst duration. With blocking of both GABA_A and GABA_B receptors, there is excessive and prolonged burst activity in both the “ON” and “OFF” phases with loss or attenuation of the normal “PAUSE” phase (80) (Figure 3).

GABAergic SLSC inter-neurons, following a visual stimulus, activate GABA_A receptors and limit the duration of both “ON” and “OFF” responses (81, 82). GABAergic inhibition of activity in excitatory neurons prevents unnecessarily prolonged burst activities in the SLSC local circuit, which affects the burst firing in the DLSC through direct signal transmission from the superficial to the deeper layer of the SC (24, 81, 83, 84). This mechanism may endow the SLSC with the ability to detect the appearance, but not the persistent presentation, of an object in the visual field, allowing the SLSC to function as a saliency detector, which might be modulated by cholinergic inputs (85).
FIGURE 3 | Discharge properties of the wide field vertical cells in the superficial laminae of the superior colliculus: GABA(A) and GABA(B) receptors cooperatively shape transient “ON” responses. (A) A typical WFV cell is illustrated in the SGS and SO; both form part of the superficial laminae of the superior colliculus, contacting a premotor neuron (in red) in the SGI (part of the DLSC). Inset: small-scale drawing of same section. (B) Typical ON–PAUSE–OFF pattern response in a WFV cell to a static visual stimulus lasting 300 ms. Five traces are superimposed. The inset shows the expanded trace of a single spike with a positive–negative sequence due to close apposition of the recording electrode to the cell. Gray-shaded areas in the panels indicate duration of visual stimulus presentation. (C) Local application of the GABA(A) receptor antagonist significantly increased the peak-firing rate but did not affect “ON” response duration. (D) Local application of the GABA(A) receptor antagonist significantly prolonged the “ON” response duration, but did not affect the peak-firing rate. (E) Local application of both GABA(A) and GABA(B) receptor antagonists significantly increased the peak-firing rate and prolonged the “ON” response duration. Figure adapted from an original study kindly provided by Professor Tadashi Isa, from Ref. (80) with permission. GABA, gamma-aminobutyric acid; WFV, wide field vertical; SGS, stratum griseum superficiele; SGI, stratum griseum intermediale; SO, stratum opticum; DLSC, intermediate and deep laminae of the superior colliculus.

MECHANISM OF ABNORMAL TEMPORAL DISCRIMINATION IN DYSTONIA
Excessive firing in both the “ON” and “OFF” phases of the visual response in the SLSC and the consequent reduction of the “PAUSE” phase, caused by loss of GABA inhibition, results in increased discharge duration and loss of sharpness of the offset of the neuronal response (Figure 3). The effect of the increased duration of both the “ON” and “OFF” phases of the discharge in the WFV cells would increase the duration of the inter-stimulus interval before two asynchronous stimuli would seem, to the observer, as being separate in time. Thus, we postulate that impaired GABAergic activity in the SLSC would result in an inability to discriminate two visual stimuli in short succession and result in abnormal (prolonged) temporal discrimination.

CONTROL OF CEPHALOMOTOR OUTPUT FROM THE SUPERIOR COLLICULUS
DISINHIBITION OF THE SUPERIOR COLLICULUS AND CEPHALOMOTOR NEURONS
The vertical interlaminar connection from the SLSC to the DLSC requires disinhibition from the GABAergic system for the signal to transmit in the pathway (24, 86) (Figure 4). The relationship between GABAergic inhibition from the SNpr and the intrinsic GABAergic inter-neurons of the superior colliculus has been examined by Isa and his colleagues. Neuroanatomical studies have shown that SNpr input to the superior colliculus contacts both glutaminergic motor cells in the DLSC and GABAergic inter-neurons. GABA(B) receptor activation limits both the burst duration of the visual cells in the SLSC and the premotor neurons in the DLSC. Importantly, prolonged bursts in the visual sensory cells in the SLSC, caused by GABA(B) receptor blockade, are necessary for the generation of long-lasting bursts in the premotor neurons in the DLSC (Figure 4) (81, 82).

DISINHIBITION OF THE SUPERIOR COLLICULUS IN THE GENERATION OF EXPERIMENTAL CERVICAL DYSTONIA IN PRIMATES
In monkeys, experimental evidence has shown over the last 25 years that (a) unilateral SNpr lesions induced head turning/tilting to the opposite side (38), (b) muscimol (a GABA agonist) injection into the left SNpr induced a severe contralateral torticollis in 10/12 injections (87), and (c) intranigral muscimol induced a contrateral directed torticollis from central and posterior sites of the SNpr in 3/3 monkeys (88).
A core neurophysiological feature of dystonia is reduced inhibition at all levels of the CNS; the most probable cause of this is defective GABAergic inhibition (90). It thus might be reasonably postulated that the link between abnormal temporal discrimination and cervical dystonia is reduced GABAergic inhibition affecting the superior colliculus. Such impaired inhibition results in increased excitability and abnormal burst firing of visual sensory neurons in the SLSC; the subsequent increased excitability of the cephalomotor cells of the DLSC causes experimental cervical dystonia. Thus, it would be reasonable to postulate that abnormal temporal discrimination in both patients with cervical dystonia and their unaffected first-degree relatives is a subclinical marker of defective GABA inhibition in the superior colliculus.

**CEREBELLAR LESIONS, DYSTONIA, AND TEMPORAL DISCRIMINATION**

The role of cerebellar lesions in the genesis of secondary dystonia including cervical dystonia and blepharospasm has been recently highlighted (91, 92). Temporal discrimination is abnormal in cerebellar degeneration (93). It is likely that inputs from the cerebellum modulate the intrinsic microcircuit of the superior colliculus but the mechanisms have not been examined in animal models.

**CLINICAL EVIDENCE OF ABNORMAL HEAD-TURN CONTROL IN CERVICAL DYSTONIA**

In the last few years, a number of investigators have demonstrated abnormalities in head control and head turning in cervical dystonia. Given the difficulties with rapid alternating movements seen in dystonic muscles, this might not be unexpected. However, saccade delays, head on trunk bradykinesia, and truncal bradykinesia, exceeding that found in Parkinson’s disease, are seen in cervical dystonia (94). Oculomotor function is normal in cervical dystonia but gaze control (combined head and eye movement) is defective because abnormal head turning interferes with saccadic function. A number of investigators have implicated the midbrain interstitial nucleus of Cajal in this defective mechanism (95, 96) but the preponderance of the experimental evidence described above indicates that defective inhibition within the superior colliculus and from the SNpr, disrupting the midbrain attentional orienting network, is the more probable mechanism of disease pathogenesis in cervical dystonia.

**OTHER LATE-ONSET FOCAL DYSTONIA PHENOTYPES**

Most work quoted in this study has addressed cervical dystonia and the cephalomotor system. However, it is likely that all the adult-onset focal dystonia phenotypes share similar etiological factors and pathogenic mechanisms (97). Anatomical studies indicate that premotor neurons originating in the DLSC form part of the tecto-reticulospinal and tectospinal tracts, and may affect facial, bulbar, forearm, and hand muscles, and thus be implicated in the genesis of cranial and focal hand dystonias (69, 76, 98–101) (Figure 2). Certainly abnormal temporal discrimination is found in all these focal dystonia phenotypes suggesting that similar pathogenic mechanisms may be involved (7, 102, 103).

**CONCLUSION**

We postulate that cervical dystonia and abnormal temporal discrimination are both due to a disorder of the midbrain network for attentional orienting, caused by impaired GABAergic mechanisms of inhibition of sensorimotor processing within the superior colliculus. This deficiency in GABAergic activity results in abnormal burst firing in the visual sensory cells in the superficial laminae of the superior colliculus, and thus the abnormal temporal discrimination found in patients with cervical dystonia and their

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**FIGURE 4** | The microcircuit of the superior colliculus. Reduced GABA inhibition causes pronged burst duration firing in both the sensory and premotor neurons. A postulated mechanism for both abnormal temporal discrimination and cervical dystonia. Diagram of the local circuit underlying GABA receptor-mediated regulation of bursts in the superior colliculus (adapted from an original study kindly provided by Professor Tadashi Isa, from Ref. [82]). Post-synaptic GABA receptors expressed in both NFV and WFV cells and presynaptic GABA receptors located on glutamatergic synaptic terminals in the SLSC are activated by synaptically released GABA during bursts of SLSC GABAergic neurons. GABA receptor inhibition normally curtails the discharge of both the sensory and premotor neurons. When GABA receptors are blocked, burst duration in sensory neurons, the SLSC, may be prolonged in an NMDA receptor-dependent manner. Under conditions of reduced GABA inhibition, this prolonged bursting may spread to the DLSC involving the oculomotor and cephalomotor premotor neurons. This prolonged bursting is postulated to result in excessive cephalomotor neuronal activity and result in cervical dystonia. DLSC, intermediate and deep laminae of the superior colliculus; oculomotor & cephalomotor premotor neurons.

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Further to their initial experiments, Karen Gale’s group examined the effect of blocking the DLSC (89). In four macaques pretreating the DLSC with muscimol, before lesioning the SNpr in the same animal, prevented or attenuated the development of the experimentally induced cervical dystonia (laterocollis in three animals and torticollis in one). Thus, reduction of the inhibitory GABAergic input from the SNpr to the DLSC in macaques causes a movement disorder resembling cervical dystonia. Blocking the motor output from DLSC by pretreating the superior colliculus prevents the movement disorder (89).
unaffected first-degree relatives. Prolonged duration firing of the visual sensory neurons is a necessary prior abnormality for the development of the hyperexcitability of the premotor neurons in the DLSC. These hyperexcitable DLSC premotor neurons, via the tecto-reticulospinal and tectospinal pathways, stimulate motor neurons in the upper cervical spinal cord resulting in the abnormal, jerky head spasms characteristic of cervical dystonia.

PROBLEMS AND FUTURE SOLUTIONS

Clearly, this hypothesis does not explain the cause of the defective GABAergic inhibition in the superior colliculus. It is likely that processes upstream in the basal ganglia in relation to dopamine processing and disordered D1/D2 receptor availability are responsible [reviewed in Ref. [104]].

In order to advance this hypothesis, a number of experiments are required. These experiments include: (a) examination of the visual response to salient stimuli in the neck muscles in patients with cervical dystonia and in their unaffected first-degree relatives with abnormal and normal temporal discrimination. (b) Examination of the fMRI response to looming stimuli in the superior colliculus in both patients with cervical dystonia and their unaffected relatives with and without abnormal temporal stimulation. (c) Magnetic resonance spectroscopic examination studies are needed for levels of GABA in the superior colliculus in patients with cervical dystonia and their relatives with and without abnormal temporal discrimination.

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