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Review

The functional neuroanatomy of dystonia

Vladimir K. Neychev [a], Robert E. Gross [b], Stephane Lehéricy [c], Ellen J. Hess [d], H.A. Jinnah [e,*]

[a] Department of Surgery, Danbury Hospital, CT, USA
[b] Departments of Neurosurgery and Neurology, Emory University, Atlanta, USA
[c] Service de Neuroradiologie, Centre de Neuroimagerie de Recherche-CENIR, CR-ICM, Hopital Pitie-Salpetriere, Université Pierre et Marie Curie, Paris, France
[d] Departments of Pharmacology & Neurology, Emory University, Atlanta, USA
[e] Departments of Neurology, Human Genetics, & Pediatrics, Emory University, Atlanta, USA

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ABSTRACT

Dystonia is a neurological disorder characterized by involuntary twisting movements and postures. There are many different clinical manifestations, and many different causes. The neuroanatomical substrates for dystonia are only partly understood. Although the traditional view localizes dystonia to basal ganglia circuits, there is increasing recognition that this view is inadequate for accommodating a substantial portion of available clinical and experimental evidence. A model in which several brain regions play a role in a network better accommodates the evidence. This network model accommodates neuropathological and neuroimaging evidence that dystonia may be associated with abnormalities in multiple different brain regions. It also accommodates animal studies showing that dystonic movements arise with manipulations of different brain regions. It is consistent with neurophysiological evidence suggesting defects in neural inhibitory processes, sensorimotor integration, and maladaptive plasticity. Finally, it may explain neurosurgical experience showing that targeting the basal ganglia is effective only for certain subpopulations of dystonia. Most importantly, the network model provides many new and testable hypotheses with direct relevance for new treatment strategies that go beyond the basal ganglia. This article is part of a Special Issue entitled "Advances in dystonia".

Contents

* Corresponding author at: Woodruff Memorial Building Suite 6000, 101 Woodruff Circle, Atlanta GA, 30322, USA. Fax: +1 404 712 8576.
E-mail address: hjinnah@emory.edu (H.A. Jinnah).
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Introduction

Dystonia is defined as a syndrome of involuntary sustained or intermittent muscle contractions leading to twisting or repetitive movements or abnormal postures (Fahn, 1984; Fahn, 1988). The core problem involves over-contraction of the primary muscles normally used for a movement, along with over-flow contraction of nearby muscles that sometimes antagonize the primary muscles. The patterns and strengths of the muscles involved determine the character of the resulting abnormal movement. Very mild dystonias appear as slight exaggerations or distortions of otherwise normal movements. More obvious manifestations include movements that are overtly stiff, slow, twisting, or jerky. The most serious expressions involve unnatural postures or fixed deformities associated with significant disability.

Virtually any region of the body may be affected, and the region affected provides a convenient means for subgrouping (Fahn, 1988; Geyer and Bressman, 2006; Tarsy and Simon, 2006). Focal dystonias involve an isolated body region. Commonly recognized focal dystonias include the neck in cervical dystonia (torticollis), the upper face (blepharospasm), the larynx (spasmodic dysphonia), or a limb (writer's cramp). Segmental dystonias involve two or more contiguous body regions, such as the neck and one arm. Multifocal dystonias involve two or more non-contiguous regions, while generalized dystonias encompass a broad distribution.

The dystonias also can be grouped according to etiology, with both inherited and acquired forms (Bressman, 2003; deCarvalho Aguiar and Ozelius, 2002; Nemeth, 2002). Dystonia is associated with mutations in more than 30 different genes, is a feature of several neurodevelopmental or neurodegenerative disorders, and can arise from a vast array of acquired insults to the nervous system. Traditionally, etiological subgroups of dystonia have included primary dystonia, dystonia-plus syndromes, developmental or degenerative disorders, and acquired insults. Primary dystonias include disorders where dystonia is a relatively isolated neurological problem and there is no histopathological evidence for developmental or degenerative anomalies. Many primary dystonias are idiopathic, but some are due to known genetic defects. The dystonia-plus syndromes include dystonia with other neurological problems, again without significant histopathological correlates. In contrast, the developmental and degenerative syndromes include specific histopathological hallmarks. Acquired forms are defined by specific causes; some have histopathological correlates (e.g. stroke or traumatic brain injury), while others do not (e.g. drug-induced dystonias).

The current review addresses regions of the nervous system underlying the dystonias. Delineating the functional neuroanatomical substrates for dystonia is of fundamental importance for both clinical and basic research. Knowing the responsible brain regions is a prerequisite for more precise studies of neuronal physiology and biochemistry, and for designing both medical and surgical treatment strategies. In keeping with currently used definitions of dystonia, this review focuses on dystonia as a syndrome of abnormal movements, not a specific disease entity. Although etiological heterogeneity raises the possibility that different dystonias may have different neuroanatomical substrates, the working premise is that some dystonias share common biological substrates (Defazio et al., 2007; Jinnah and Hess, 2008).

Historical perspective

Historically, delineating a new neurological disease as a distinct nosological entity required linking specific clinical features with consistent neuropathological changes. Hammond was among the first to describe pathology of the basal ganglia in an individual with athetosis (Hammond, 1890), a diagnosis that historically overlapped with dystonia (Morris et al., 2002; Salam-Adams and Adams, 1997; Twitchell, 1961). Hammond's report stimulated others to focus on the basal ganglia, but results were inconsistent. Most notable was the absence of consistent pathology in cases with pure dystonia, now designated as primary dystonias. It was the failure to establish consistent clinico-pathological correlations that led to the rejection of pure dystonia as a neurological disorder at the 10th International Neurological Meeting in 1929 (Wimmer, 1929).

The view that pure dystonia was a psychiatric disorder prevailed for nearly five decades, but some investigators continued to find evidence for an organic basis (Munts and Koehler, 2010). In one of the earliest reviews on the neuropathology of dystonia that included 17 affected individuals, Herz cataloged abnormalities in the putamen, caudate, pallidum, and thalamus (Herz, 1944). Herz emphasized the organic nature of some dystonias, disregarding pure forms where pathology was not apparent. In subsequent studies, Zeman distinguished two subclasses of dystonias (Zeman, 1970). Overt basal ganglia pathology was frequent among those with dystonia secondary to another disorder such as Wilson's disease, kernicterus, perinatal injuries or ischemic lesions. Pathology was not evident in pure dystonias, which he viewed as disorders of biochemistry or function.

These early neuropathological studies have played a dominant and enduring role in modern concepts regarding the neural substrates of dystonia. Today, many investigators work under the premise that dysfunction of the basal ganglia is responsible for *all* forms of dystonia. This premise is evident in experimental studies that focus exclusively on the basal ganglia, in studies that dismiss changes in other brain regions as epiphenomenal, in reviews that exclusively summarize evidence relating to the basal ganglia, and in descriptions of dystonia that imply dysfunction of the basal ganglia is a defining characteristic. In fact, some writers use the term “pseudodystonia” for dystonic movements that do not have their origin in basal ganglia dysfunction. However, modern definitions of dystonia are based on the nature of abnormal movements without presuming any specific neuropathological substrate. This review encompasses evidence relating to any brain region that may be relevant for dystonic movements.

The basal ganglia in dystonia

Evidence for involvement of the basal ganglia

The evidence supporting a role for the basal ganglia in dystonia is strong; but it will be summarized here only briefly, since it has been reviewed many times by others (Berardelli et al., 1998; Breakefield et al., 2008; Hallett, 2006). As noted above, the role of the basal ganglia originated with studies showing neuropathological defects in the basal ganglia of individuals with various secondary forms of dystonia (Hedreen et al., 1988; McGeer and McGeer, 1995). These early studies later were supported by results from neuroimaging including CT or MRI, where focal lesions often were found in the basal