

Are Cognitive Symptoms Part of the Phenotypic Spectrum of Idiopathic Adult-Onset Dystonia? Summary of Evidence from Controlled Studies

Giovanni Defazio, MD, PhD,¹ Antonella Muroi, MD, PhD,^{2,*} Paolo Taurisano, PsyD,¹ Angelo Fabio Gigante, MD, PhD,³ Michela Fanzecco, PsyD,⁴ and Davide Martino, MD, PhD⁵

Abstract: Background: Cognitive dysfunction has been reported in idiopathic adult-onset dystonia (IAOD), but whether this is a primary or secondary component of the disorder remains uncertain.

Objective: Here, we aimed to analyze the key domains of abnormal cognitive performance in IAOD and whether this is associated with motor or mood changes.

Methods: Article selection for our critical review was guided by PRISMA guidelines (mesh terms “dystonia” and “cognitive,” publication period: 2000–2022). Only peer-reviewed, English-language original case-control studies involving patients with IAOD who were not exposed to dopamine- or acetylcholine-modulating agents and validated cognitive assessments were included.

Results: Abstract screening ultimately yielded 22 articles for full-text review and data extraction. A greater proportion of studies (17 of 22, 82%) reported abnormal cognitive performance in IAOD. Most of these studies focused on blepharospasm (BSP) and cervical dystonia (10 and 14, respectively). Most studies reporting cognitive impairment (11 of 17) identified multidomain impairment in cognition. Executive functions were the domain most frequently explored (14 of 22 studies), 79% of which detected worse performance in people with dystonia. Results related to other domains were inconclusive. Cognitive abnormalities were independent of motor symptoms in most studies (7 of 12) that explored this relationship and independent of mood status in all 8 that investigated this.

Conclusions: Within IAOD, cognitive dysfunction (in particular, executive dysfunction) has been documented mainly in BSP and cervical dystonia. More comprehensive testing is warranted to assess abnormalities in other domains and in other forms of IAOD, as well as to evaluate longitudinal progression of cognitive disturbances in this condition.

A conspicuous body of evidence indicates that people with idiopathic adult-onset dystonia (IAOD), the most common form of dystonia,¹ exhibit a diverse spectrum of nonmotor manifestations that include pain and other sensory signs and symptoms, sleep disturbances, and neuropsychiatric symptoms (mainly anxiety and depression).^{2,3} In the past 2 decades, a growing literature has

extended the focus also to cognitive abnormalities. These studies yielded mixed results,⁴ probably because of considerable methodological variation among studies. Prominent sources of heterogeneity across these studies were the diverse array of neuropsychological test batteries used and the variability in dystonia forms and subtypes assessed across studies. Despite the

¹Department of Translational Biomedicine and Neuroscience, Aldo Moro University of Bari, Bari, Italy; ²Section of Neurology, University Hospital, Cagliari, Italy; ³Section of Neurology, San Paolo Hospital, Bari, Italy; ⁴Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; ⁵Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

*Correspondence to: Dr. Antonella Muroi, Section of Neurology, University Hospital, Cagliari, Italy; E-mail: antonellamuroi79@gmail.com; amuroi@aoucagliari.it

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Giovanni Defazio and Antonella Muroi have contributed equally to this study.

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recognized physiological relevance to cognition of the brain circuitry associated with dystonia (cortico-basal ganglia networks, cerebello-thalamo-cortical, and cerebello-thalamo-basal ganglia circuits), it remains undetermined whether cognitive dysfunction represents a primary or a secondary phenotypic component of the disorder. Indeed, it is plausible that some cognitive deficits might occur as a consequence of the distracting effects of the core motor features of dystonia.⁵ Nonmotor features of dystonia, particularly depression and anxiety, are also established major confounders of cognitive performance, although the impact of this confounding on cognition has not been properly evaluated by previous observational studies.

To provide a comprehensive analysis of the presence of cognitive impairment in dystonia and the relationship of altered cognition with dystonia subtypes, motor symptom severity, and mood disturbances, we reviewed case-control studies in which cognitive functions were directly compared between people with dystonia and healthy individuals. This review aimed to address the following questions. Do people with dystonia manifest abnormal cognitive performance? How does abnormal cognitive performance manifest across the different forms of IAOD, and which are the most frequently involved cognitive domains? Are cognitive abnormalities in people with IAOD associated with motor features of dystonia or with concurrent anxiety and/or depression?

We highlighted areas of more consistent findings, as well as those in need of greater study, aiming to increase awareness of the unmet clinical need related to cognition in dystonia, and direct future investigations.

Patients and Methods

To conduct this review, we were guided by the standardized PRISMA guidelines in the selection of relevant articles. Our eligible population of interest included adult subjects with a diagnosis of idiopathic dystonia, based on the MDS Task Force Classification of dystonia, who were not on dopamine-modulating or anticholinergic therapies.

The search was carried out in the PubMed and EMBASE databases, with reference to publication time ranging from January 1, 2000, to December 31, 2022. The search strategy and the selection criteria are shown in Figure 1. The mesh terms “dystonia” and “cognitive” included in the title and/or abstract were used for the search.

Screening of unique records followed a two-stage process. In the first stage, we screened by title/abstract to select only peer-reviewed, English-language original research studies that enrolled individuals aged 18 years or above. Uncontrolled studies, systematic reviews with related meta-analyses, any other types of review article, and case reports were excluded in this stage. Pilot testing of the first 100 retrieved titles and abstracts led to sufficient agreement between 2 reviewers (G.D. and A.M.). In the second stage of screening, titles/abstracts of the remaining papers were reviewed

for potential relevance by 1 reviewer (G.D.) using the following inclusion criteria: diagnosis of idiopathic dystonia; presence of control group(s); and use of validated, non-experimental cognitive tests. The full texts of the selected articles were then reviewed, which led to the exclusion of a further subgroup of these articles and data extraction from the final list of selected articles. The latter were all case-control studies reporting on formal assessment of cognitive functions in case patients with IAOD and healthy controls, in the absence of concomitant therapy with dopaminergic and anticholinergic medication.

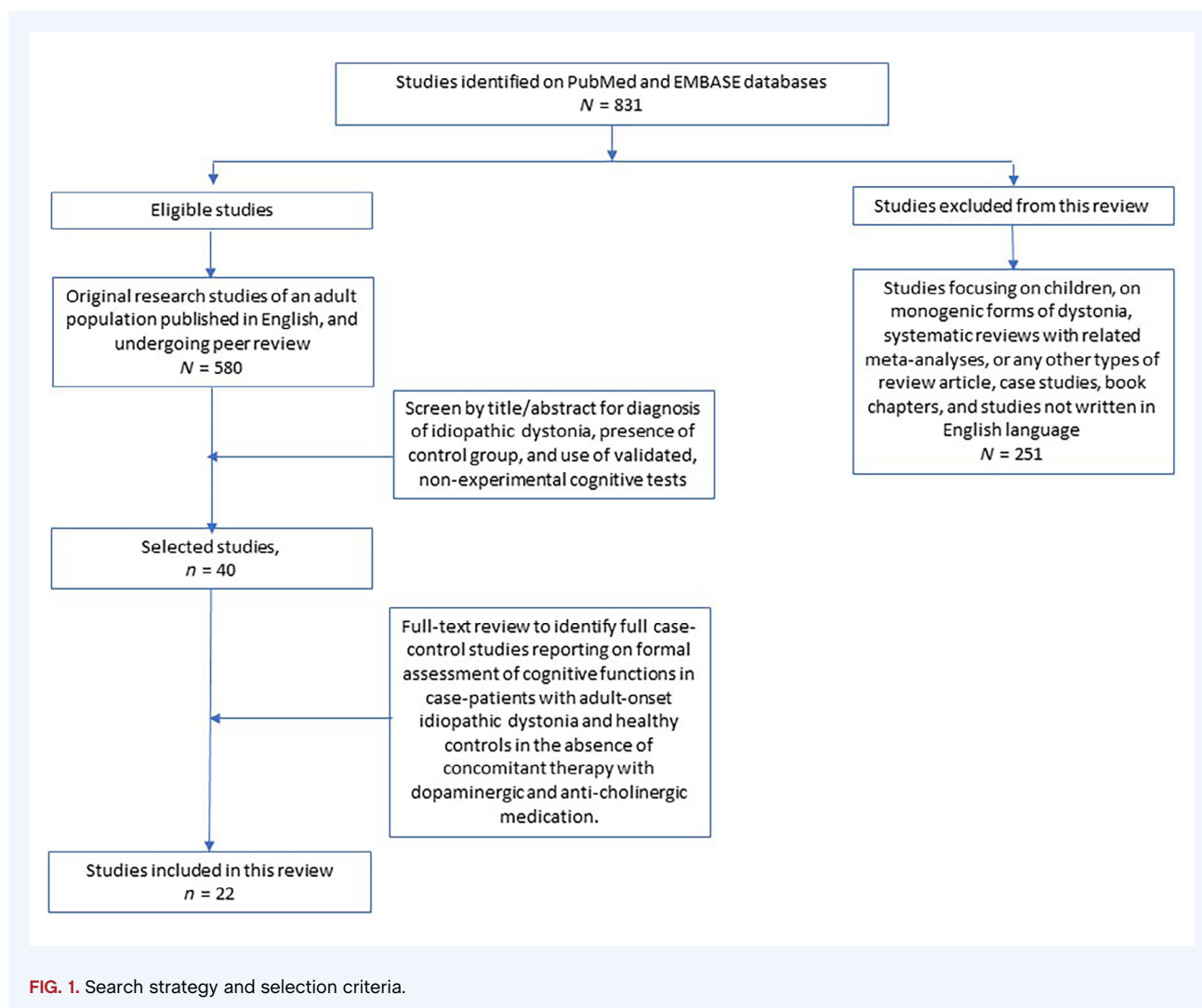
The following information was extracted from the final list of selected articles: sample size, study subgroups, cognitive outcome (ie, test name) and correspondent domain (eg, learning, memory), study outcome (whether dystonia patients performed worse than or equal to healthy controls), and adjustment, if any, for severity of motor symptoms and/or psychiatric disturbances. Comparisons among groups were performed using *t* test.

Results

Our search (Fig. 1) yielded 831 titles, of which 580 satisfied the eligibility criteria (Fig. 1). The 580 references were screened by title and abstract, thus leading to the selection of 40 articles that were finally evaluated through full-text review for data extraction. After full-text review, we identified 22 full papers^{6–27} comparing cognition between people without and healthy controls in the absence of concomitant therapy with dopaminergic and anticholinergic medication, which were therefore used for data extraction. Figure S1 shows graphically the years of publication for all the 22 selected articles.

Do People with Dystonia Manifest Abnormal Cognitive Performance?

The data extracted from the 22 selected studies are summarized in detail in Table S1. People with dystonia performed significantly worse than healthy controls in 18 studies^{6–14,17–21,23,25–27} and not significantly different from healthy controls in 4.^{15,16,22,24} Therefore, we observed a nonsignificant trend for a greater proportion of studies reporting abnormal cognitive performance in people with dystonia (82% vs. 18%, $P = 0.07$). The mean number of case patients was significantly larger in studies reporting worse performance in people with dystonia than in those that did not (mean number of patients $\pm$ SD [standard deviation], 44.8 ± 26.4 vs. 20.5 ± 11.5 , $P = 0.045$). Mean case-control ratio $\pm$ SD was close to 1 in those studies that reported abnormal cognitive performance in people with dystonia as in those that did not (1.16 ± 0.41 vs. 0.92 ± 0.09 , $P = 0.2$). The majority of studies reporting abnormal cognitive performance in people with dystonia (15 of 18, 83%^{8,10,17–21,23,25–27}), but also a relevant proportion of the other studies (2 of 4, 50%^{15,24}), were



published in the past 10 years, which probably makes a publication bias unlikely.

How Does Cognitive Impairment Manifest across the Various Forms of Dystonia?

Most of the 22 selected studies focused on the most frequent forms of adult-onset dystonia, that is, blepharospasm (BSP, 10 studies^{6,7,9,13,18,20,23–26}) and cervical dystonia (CD, 14 studies^{8–12,14,15,17,19,20,22,23,25,27}), either alone or combined; 3 studies also included patients with generalized dystonia.^{14,16,21} All 10 studies that enrolled people with BSP, 12 of 14 studies that enrolled people with CD,^{8–12,14,17,19,20,23,25,27} and 2 of 3 studies that enrolled people with generalized dystonia^{14,21} reported worse cognitive performance in people with dystonia compared to healthy individuals.

What Are the Most Affected Cognitive Domains across All Forms of Dystonia?

Most studies (21 of 22) explored several cognitive domains in the same study (eg, executive functions, global functioning, attention, language, memory, praxis, visuospatial skills, and time–space orientation; see also Table S1), and 17 showed differences between people with dystonia and healthy controls. Of 17 studies, 5 showed impairment in a single cognitive domain,^{7–9,14,20} whereas 11 studies were characterized by multidomain impairments in cognition.^{6,10–13,19,21,23,25–27} We could not check for differences in disease duration and age at dystonia onset because only 4 studies reporting cognitive impairment^{11,13,25,26} and 1 that did not¹⁶ provided this information.

In addition to extended neuropsychological test batteries, some studies on BSP and CD demonstrated cognitive abnormalities in people with dystonia using brief global cognitive

TABLE 1 Proportion of the selected studies in which each of the explored cognitive domain was assessed and proportion of studies that demonstrated worse performance on that cognitive domain in people with dystonia compared to healthy controls

Cognitive domain	Number of papers (%)	Number of papers detecting worst performance in dystonia (%)
Executive functions	14/22 (64%)	11/14 (79%)
Global functioning	13/22 (59%)	5/13 (38%)
Attention	12/22 (54%)	7/12 (58%)
Language	11/22 (50%)	6/11 (54%)
Prospective memory/retrospective memory	10/22 (45%)	5/10 (50%)
Praxis	9/22 (41%)	4/9 (44%)
Visuospatial skills/visuospatial memory	3/22 (14%)	2/3 (67%)
Time–space orientation	3/22 (14%)	2/3 (67%)
Verbal working memory	3/22 (14%)	2/3 (67%)
Apathy	1/22 (4.5%)	0/1
Theory of mind	2/22 (9%)	1/2 (50%)

assessment instruments.^{8,11,13,15,22,24–26} Two studies used the Mini-Mental State Examination (MMSE),^{8,26} 5 studies used Montreal Cognitive Assessment (MoCA),^{11,13,15,22,24} and 2 studies used Addenbrooke’s Cognitive Examination-Revised (ACE-R).^{25,26} Cognitive impairment could be identified by MMSE in 1 of 2 studies,²⁶ by MoCA in 2 of 5 studies,^{11,13} and by ACE-R in 2 of 2 studies.^{25,26} In 1 study comparing 2 such scales in the same population of BSP patients, the prevalence of cognitive deficits was 22.0% and 32.3%, as measured using MMSE and the ACE-R, respectively.²⁶

Table 1 summarizes the proportion of the selected studies in which each of the explored cognitive domain was assessed and the proportion of studies that demonstrated worse performance on that cognitive domain in people with dystonia compared to healthy controls. “Executive functions” was the only domain that was examined by a relatively large number of studies (14 of 22), most of which (79%) detected worse performance in people with dystonia than in healthy controls. The results of the other domains should be considered as inconclusive, either because they were assessed by a small number of studies (visuospatial skills, visuospatial memory, temporal–spatial orientation, verbal working memory, prospective memory/retrospective memory, apathy, and theory of mind were explored by 1–3 studies) or because results were inconsistent across studies (impaired attention, global functioning, language, and praxis were observed only in 35%–54% of studies). We were aware that checking for the extent of cognitive impairment by the proportion of studies demonstrating worse performance in people with dystonia might have disguised some of the nuances of the research. Given the wide variability and the range of quality in the reviewed studies, however, this could be a simple, though coarse, way to identify the most involved domains.

Are Cognitive Deficits Associated with Motor or Other Nonmotor Symptoms of Dystonia?

Altered cognitive performance was independent of motor symptoms in 8 of 13 studies that assessed the relationship between cognitive impairment and severity of dystonia.^{6,9,10,13,14,23,25,26} Some papers also took into account the possible confounding effect of psychiatric problems in relation to measures of cognitive performance^{6,9,10–12,14,19,26}; in particular, 2 studies excluded patients with psychiatric problems,^{11,12} whereas the remaining 5 studies either controlled for psychiatric problems^{6,10,14,26} or failed to find any correlation between cognitive performance and severity of psychiatric problems.^{9,19}

Discussion

Although the body of evidence is not large, most selected case–control studies showed that patients with dystonia may perform worse than healthy controls in several cognitive tasks. The 4 studies that yielded no difference in cognition between case and controls were characterized by a smaller sample size, thus suggesting that their negative findings could depend on low statistical power. Altered cognitive performance was independent of motor symptoms in 7 of 10 studies that assessed the relationship between cognitive impairment and severity of motor symptoms. In addition, some studies checked for possible influence of anxiety and depression on the association between altered cognitive performance and case status, but no appreciable confounding effect could be detected.^{6,9,10,14,19} This would suggest against the hypothesis that

cognitive impairment is secondary to motor features (dystonia or tremor) or depression. Available data therefore indicated that mild cognitive impairment may be a feature associated with IAOD.

From our literature review, a variety of limitations of the body of evidence published so far emerge. As highlighted earlier, a small sample size is not uncommon, with 8 of the 22 selected studies reporting on dystonia groups of <20 patients. To date, cognitive dysfunction has mainly been documented in patients with idiopathic BSP and CD. Data on other forms of IAOD were limited and often inconclusive. Importantly, although several cognitive domains were investigated in patients with dystonia, only executive functions seem to be consistently associated with this movement disorder, whereas the available evidence is markedly inconsistent and inconclusive in relation to the other cognitive domains. Even if cognitive performance was not associated with motor severity in the majority of reports that assessed this, most of the selected studies failed to analyze this. Lack of assessment is an even more striking limitation when considering a potential interrelationship between cognitive performance and the highly prevalent mood and anxiety symptoms in IAOD, with only 5 studies reporting on this aspect. Sleep disruption is also common in IAOD, but how poor quality of sleep, altered sleep architecture, and excessive daytime sleepiness influence cognitive performance in IAOD remains unexplored. Future studies evaluating the association between cognitive performance and motor or other nonmotor symptom severity in IAOD should also take into account the exact time within botulinum toxin treatment cycles in which patients are tested, because this may also influence the association. Finally, the studies selected by our critical review shared a cross-sectional approach and did not provide enough information to test whether studies characterized by impairment in a single or multiple domains differed for age at dystonia onset or disease duration. Therefore, the available evidence does not allow any conclusion on whether cognitive impairment in dystonia is likely to worsen over time.

The emerging picture of cognitive impairment in dystonia may have a biological plausibility, particularly if we consider the current viewpoint that dystonia arises from abnormalities in a motor network that includes the basal ganglia, thalamus, cerebellum, frontal and parietal cortex, and possibly other cortical regions.^{28,29} This broad network may be affected in different ways across different individuals or forms of dystonia, with some regions contributing more than others to the specific cognitive abnormalities reported thus far. Dysfunction within these circuits has been linked to impairments in memory, spatial attention, and executive functions in other disorders with prominent basal ganglia involvement, above all Parkinson's disease.^{30,31} In dystonia, isolated deficits in semantic fluency, set shifting, and attention have been postulated to be reflective of executive function deficits arising from dysfunction within fronto-striatal circuits.³² Increasing attention is being paid to the cerebellum, a region historically linked to motor function that has multiple cortical connections to the thalamus and the prefrontal cortex. Neuropsychological studies suggest that dysfunction in the cerebellum itself or its networks may be associated with visuospatial, attention, language, memory, and executive function deficits.³³ In CD, reduced cerebellar activation and subsequent reduced

connectivity to the basal ganglia and motor cortical areas were observed during the execution of a visuospatial task.³⁴ It is worth noting that some of the brain areas involved in the pathophysiology of dystonia also contribute to the dorsal attention network, a system that is engaged during externally directed attentional tasks and comprised widely scattered computation nodes in different cortical and subcortical regions.³⁵

Overall, data summarized by our critical review suggests that cognitive impairment is probably part of the phenotypic spectrum of IAOD, at least in a proportion of patients. Cognitive dysfunction has mainly been documented in patients with idiopathic BSP and CD and is probably independent of the severity of motor symptoms and mood status. Executive functions seem to be the main affected cognitive domain. Our analysis also highlights areas in need of greater investigation and suggests directions for future study. In this regard, several points can be made. Further and more comprehensive cognitive testing, focusing more on domains other than executive functions and on generalized forms of dystonia, is necessary to better understand the extent of cognitive impairment in the various forms of dystonia. This warrants the use of extended and comprehensive neuropsychological test batteries in selected, homogeneous, and relatively small groups of patients assessed cross-sectionally. Another crucial, yet unanswered question is the frequency of altered cognition associated with IAOD and whether cognitive dysfunction progresses over time. To increase our ability to prognosticate cognitive impairment would require longitudinal studies in large cohorts of patients, an approach that obviously needs abbreviated tools rather than large cognitive batteries. In this regard, our revision indicated that even global, relatively simple scales such as MMSE,²⁶ MoCA,^{11,13} or the ACE-R^{25,26} may detect cognitive changes in IAOD patients, thus allowing a more routine cognitive assessment of IAOD in clinical practice. The different prevalence of cognitive deficits found using the ACE-R and MMSE in the same population suggests that the ACE-R is more sensitive than the MMSE for the detection of cognitive impairment. Finally, it would be important to assess the contribution of cognitive disturbances to the clinical subtypes that have recently been identified in cluster analyses that included motor and nonmotor symptoms.^{3,36,37,38}

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

G.D.: 1A, 1C, 2A, 2B, 3A, 3B

A.M.: 1A, 1B, 1C, 2A, 3B

P.T.: 1A, 2C

A.F.G.: 1A, 2C
M.F.: 1A, 3B
D.M.: 1A, 1B, 2C, 3A, 3B

Disclosures

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Supporting Information

Supporting information may be found in the online version of this article.

FIG S1. Number of studies per year comparing cognition between people with idiopathic adult-onset dystonia and healthy controls (2000–2022).

Table S1. Summary data from 22 case-control studies comparing cognitive performance in patients with idiopathic adult-onset dystonia and healthy controls.