CHAPTER

What can kinematic studies tell us about the mechanisms of dystonia?

19

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Abstract

Clinical movement disorders are classified by an algorithm implemented by a practising movement disorder specialist based on information extracted during the history and clinical examination of a patient. Most simply, dystonia, is a classifier which is reached when a predominant abnormality of posture is noted. In this chapter we summarize studies that have used a variety of techniques to probe beyond the clinical examination and study kinematic features experimentally. We also outline our experimental work in DYT1 dystonia, a group of patients that share a genetically homogenous etiology and can be considered a prototypical dystonic disorder. Our results build on previous studies, confirming that motor variability on a trial-by-trial basis is selectively increased and provide evidence that increases in variability are negatively related to forms of motor learning essential for healthy motor control. Potential neural correlates of increased motor variability are discussed and the implications such work has for the rehabilitation of patients with dystonia are also highlighted.

Keywords

Dystonia, Variability, Adaptation, Motor learning, Rehabilitation

1 Dystonia

Dystonia is a common movement disorder, which is characterized by abnormal postures of the body, often accompanied by tremor (Albanese et al., 2013). Dystonic postures are typically worsened or induced by action, are mobile and dynamic in nature and can affect specific body parts or be a generalized phenomenon. Dystonia, like many movement disorders, is the physical manifestation of a range of possible

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underlying pathologies. These range from conditions causing widespread neurodegeneration (e.g., Parkinson's disease, neurodegeneration with brain iron accumulation), discrete structural lesions (typically of the putamen), and genetic disorders where there is no overt degenerative change and dystonia occurs as an isolated non-progressive phenomenon. DYT1 dystonia is a paradigmatic example of this latter group and is the commonest cause of young-onset isolated dystonia (Bressman et al., 2000). It typically presents with limb dystonia in childhood or early teens, and after a period of progression to segmental/generalized involvement stabilizes and does not progress further (Weisheit et al., 2018). It is caused by a dominantly inherited three base pair deletion in the coding region of the TOR1A gene (Ozelius et al., 1999). People with DYT1 dystonia provide an ideal group within which to study the pathophysiology of dystonia. The dystonia is isolated in nature with no possible confounding effects from associated neurological deficits such as spasticity that can be found in individuals with more complex phenotypes such as dystonic cerebral palsy. Cognition is normal, and the severity of the dystonia itself is typically stable over time, after the initial period of progression is over.

2 Why study kinematics?

Research into the pathophysiology of dystonia has a long history, and the full range of investigative techniques have been applied from genetic and molecular studies, animal modeling, electrophysiology, structural and functional imaging. Broad themes have emerged from this work, for example the concept of aberrant synaptic plasticity, loss of cortical, brainstem and spinal inhibitory function. However, there is a significant difficulty in extrapolating the results of such work to create a mechanistic understanding of the movement disorder that is manifest in dystonia. Many pathophysiological "markers" of dystonia may not bear any relationship to the actual mechanism of the movement disorder itself. For example, some experimental techniques could simply document epiphenomena relating to the excess of movement observed and/or its compensation. Such arguments are supported by the general lack of correlation between the severity of specific pathophysiological markers of dystonia (e.g., cortical inhibition, aberrant plasticity) and the severity of clinical symptoms, and such abnormalities are frequently found in regions of the brain subserving unaffected body parts. Abnormal profiles of inhibition and plasticity are also found across a broad range of neurological disorders, non-specifically modulated across a range of distinct diseases.

It can therefore be argued that the study of the dystonic movement itself deserves more attention. By directly sampling the natural patterns of dystonic movement and characterizing performance within experimental tasks, one can better define kinematic signatures for dystonia and infer the nature of the motor control deficit. There remains no diagnostic test for dystonia and such work offers great potential for better clinical characterization, better severity scores for dystonia and targeted therapeutic interventions (current treatment options are relatively non-specific to pathophysiology).

3 Kinematic studies of dystonia

It is beyond this scope of this article to fully summarize the range of kinematic abnormalities that have been documented in dystonia. Instead we choose two salient and relevant themes; increased variability of movement and the apparent preservation of many motor control elements within the dystonic brain. We initially work from the premise that dystonia is a pattern of movement abnormalities or motor syndrome that can arise from a broad range of etiologies.

Since the very first kinematic studies of dystonia there has been evidence of increased variability of movement (van der Kamp et al., 1989). For example, one study compared elbow flexion movements in 10 patients with mixed etiological causes for their dystonia with controls measuring elbow flexion kinematics with a potentiometer displayed on an oscilloscope screen (van der Kamp et al., 1989). They found that even if controls are asked to match the slower dystonic movements that were observed in this study, symptomatic arms of subjects with dystonia have significantly more variability in the amplitude of their movements (quantified by the coefficient of variation) (van der Kamp et al., 1989). More recently, Fourier analysis was applied to electromyography (EMG) and kinematic data acquired during the performance of a continuous figure of eight writing task in children with dystonia and age-matched healthy controls (Lunardini et al., 2015b). This method exploited the frequency domain features of the cyclic motor task in order to discriminate between task-correlated and task-uncorrelated components of muscle activity (task-correlated at frequencies related to the cyclic figure of eight movements, task-uncorrelated components at unrelated frequencies). They confirmed their hypothesis that task-uncorrelated variability was increased in comparison to controls and argued that there was a deficit in the dystonic brain to suppress variable and uncorrelated elements of movement (Lunardini et al., 2015b).

Another feature in dystonia is that many fundamental features of motor control are intact. For example, for many years it was thought that dystonia is an abnormality of posture stemming from the co-contraction of agonist and antagonist muscles. However careful work in multi joint reaching movements using motion analysis and EMG has in fact shown that co-contraction is not an obligatory feature of multi joint movements in dystonia (Malfait and Sanger, 2007). Another line of work looks at muscle synergy patterns. The presence of muscle synergies in the healthy central nervous system is thought to reflect a general principle adopted to help the musculoskeletal system deal with inherent redundancy of motor control (the fact the we have excess resources that allows us to perform to same task in many different possible ways). Synergies, in this context are a co-ordinated activation of a group of muscles with specific activation balances defining a set of muscles working as a single functional unit. This modular organization then allows complex movements or sequences of movements to be achieved by the combination of multiple muscle synergies. Interestingly, in an analysis of performance of children with and without dystonia performing a writing task, dystonic children showed that despite the compromised kinematic outcomes of writing in dystonia, there was a strikingly similar number and structure of the synergy vectors of the two groups of children in the EMG

(Lunardini et al., 2017). Similarly, the timing of the activation of the synergy coefficients did not significantly differ (Lunardini et al., 2017). Therefore patterns of effector recruitment remain remarkably similar in this disorder with such obvious clinical motor abnormalities.

4 Variability in DYT1 dystonia

Thus in groups of dystonia due to heterogeneous etiologies increased movement variability is a core feature and many fundamental motor control features remain intact. There are some challenges in the study of mixed groups of patients. For example, studies in childhood dystonia which include dystonic cerebral palsy could also be influenced by additional, albeit lessor insults to the motor system, such as spasticity and weakness. We have therefore chosen to study variability in a homogenous patient group with the genetic DYT1 mutation in an effort to study "dystonic" motor control in isolation.

Motor variability can be defined as the normal variations that occur in motor performance across multiple repetitions of a task (Stergiou and Decker, 2011). Variability has many sources and roles (Sternad, 2018). For example, undesired variability which can potentially corrupt signal transmission with the sensorimotor system can arise secondary to noisy processes within the nervous system, anywhere from the perception of sensory stimuli through to the generation of motor responses (Faisal et al., 2008). Conversely, other types of variability appear to be informative, representing an exploration of motor command space (Tumer and Brainard, 2007). Experimentally, individuals with greater variability of baseline movement parameters relevant to the subsequent learning task are faster learners across reinforcement and motor adaption (error-based) task designs (Wu et al., 2014) (but see He et al., 2016). Moreover, features of such variability appear to be under dynamic regulation. The temporal structure of motor variability can be shown to shift responsively to align to the task design and has different characteristics across different stages of learning (Sternad, 2018; Tumer and Brainard, 2007; Wu et al., 2014). For the healthy motor system, maintaining the dynamic equilibrium of keeping unwanted variability in check while regulating informative elements which assist learning, is therefore an essential role and is an active area of motor control research. In the study of movement disorders such as dystonia understanding shifts in the profile of variability is therefore complex but highly relevant.

Using a robotic manipulandum we designed a task to examine motor variability during reaching movements in the symptomatic arm of 10 manifesting patients with DYT1 dystonia and 12 aged matched controls and investigated whether variability markers were related to motor learning (Fig. 1A) (Sadnicka et al., 2018). For every trial, participants made a fast outward movement from a central starting position toward one of four potential target positions with the aim of stopping in the target box within the fixed time frame of one second. Following a baseline block, sensorimotor adaptation was examined by applying a visuomotor perturbation which distorted

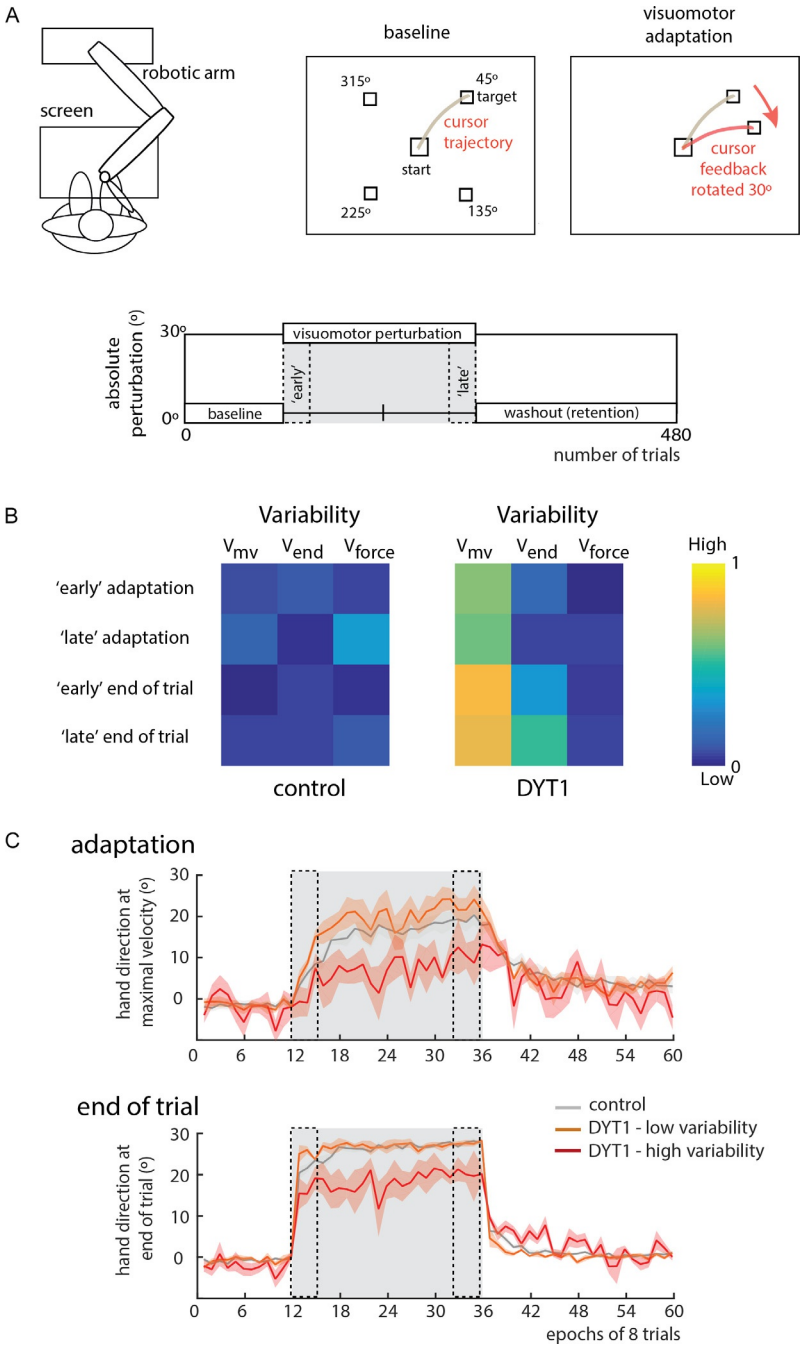

FIG. 1

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visual feedback by 30°. Veridical visual feedback was then reintroduced to examine washout (retention) of the newly learnt visuomotor rotation.

Similar to previous studies, despite the obvious dystonic movements of the symptomatic right arm we found a range of movement parameters to be within normal range. For example, the timing and magnitude of maximal velocity and the maximal force applied were not different across groups. Such findings were again suggestive of a selective motor deficit in DYT1 dystonia. More noteworthy results were found when we starting to analyze the patterns of variability of dystonic movements. Principal component analysis of the two-dimensional kinematic data (movements were made across a fixed plane) at different time points revealed that DYT1 dystonia is characterized by a subtle (yet statistically significant) increase in spatial variability. Increases in variability were maximal in phases of movement, which rely on feedforward motor control (with little or no influence of online feedback). Interestingly such variability appeared random in its nature with no directional preponderance shown in any of the reach conditions. This finding is concordant with the detailed experimental work in children which suggests that the patterns of muscle groups or muscle synergies recruited to tasks are surprisingly intact in a disorder in which the balance between different muscle groups appears so impaired (Lunardini et al., 2015a, 2017).

FIG. 1

(A) The task was displayed on a horizontal computer screen and performed using a robotic manipulandum. Each trial consisted of making a fast outward movement from a central starting position toward one of four potential target positions. The aim was to stop in the target box within the fixed time frame of one second. Following a baseline block, sensorimotor adaptation was examined by applying a visuomotor perturbation (distorting visual feedback by 30°). True visual feedback was then reintroduced to examine washout (retention) of the newly learnt visuomotor rotation. (B) We examined whether markers of variability in DYT1 dystonia influenced performance indicators in the visuomotor adaptation task. Markers of variability that we expected to be relevant to the task were (i) baseline angular variability at maximal velocity (V_{mv}) and (ii) angular variability at the end of trial (V_{end}). The baseline variability of magnitude of maximal force (V_{force}) applied was selected as a subset of variability that was less relevant to the subsequent learning task. Change of hand direction at maximal velocity (adaptation) and end of trial were used as markers of performance during "early" and "late" phases of the visuomotor perturbation. In controls, there was no obvious relationship between variability markers and performance markers. In DYT1 dystonia markers of learning were negatively correlated with task-relevant variability (V_{mv}).
(C) A median split of patients by task-relevant variability into low and high variability groups illustrates this relationship further. In the high variability group both the rate of adaptation (early) and the total magnitude of adaptation (late) were reduced. Ability to correct the visuomotor perturbation at the end of trial after the chance to also use online corrective mechanisms was also significantly negatively related to increased variability. In summary, increased variability relevant to the task was negatively correlated to adaptation performance indicators in DYT1 dystonia (see Sadnicka et al., 2018 for full experimental details).

Given that task-relevant variability and sensorimotor adaptation are related in health (Wu et al., 2014), we then examined how the increased variability in DYT1 dystonia influenced performance indicators in this adaptation learning task. Markers of trial-by-trial variability that we expected to be relevant were (i) variability of movement at maximal velocity and (ii) variability of movement at the end of trial. Variability of force applied by participants was selected as a subset of variability that was less relevant to the task. Learning metrics for both adaptation and at the end of trial (after additional online corrections) were also quantified (see detailed parameter description in legend of Fig. 1B). In controls, there was no obvious relationship between variability markers and performance with low correlation values between variability and subsequent learning metrics (Fig. 1B). In contrast in DYT1 movement variability (at maximal velocity) was clearly related to the ability to learn the visuomotor adaptation. By splitting patients into those with low and high variability this relationship is further illustrated in Fig. 1C. In DYT1 patients with high variability both the rate of adaptation (early) and the total magnitude of adaptation (late) were reduced. Ability to correct for the visuomotor perturbation at the end of trial once online corrections have occurred was also reduced. In summary, increased variability relevant to the subsequent task was negatively correlated to adaptation performance indicators in DYT1 dystonia.

This result was interesting as in health, the correlation between task-relevant variability and motor learning has been plotted as a positive linear relationship suggesting that task-relevant variability is informative to the motor system (Wu et al., 2014). If this line of reasoning is followed one interpretation is that in DYT1 dystonia, this physiological relationship breaks down. Once an upper threshold is breached increased variability no longer assists motor learning. In DYT1 dystonia, increased variability could rather introduce error and uncertainty into the control of movement leading to the poor performance observed in this study (see high variability group in Fig. 1C). Adaptation is a form or error-based learning in which the brain computes a teaching signal which is the difference between the desired movement and the actual movement (which has been perturbed by the influence of visuomotor transformation). Therefore the random spatial variability that we observed could be considered a noise factor which will be added to the teaching signal from each trial, decreasing its accuracy and certainty, and impairing the ability to compute the correction or adaptation coefficient required to update the next movement. This is one very feasible explanation of our results and such an interpretation implies that adaptation itself is intact in dystonia.

What is the relative importance and mechanism driving motor variability within disease models for dystonia? Dystonia is characterized by its involvement of a wide neuronal network and increased variability could be generated by multiple regions and multiple mechanisms. Our data and the literature are perhaps most consistent with the idea that redundant variability or noise is injected at a late phase of movement preparation. One potential neuronal correlate is the finding that there is abnormally enhanced and synchronous oscillatory activity in the *output* nuclei of the basal ganglia of patients with dystonia which is coherent with EMG activity during

dystonic movements (Barow et al., 2014; Chen et al., 2006; Liu et al., 2008). Such oscillatory activity could inject variability onto the elemental movement plan which fits with the literature in dystonia that many basic control components are intact.

It is then interesting to consider if there is evidence that the dystonic motor system is compensating for increased motor variability. In general noise cannot be removed from a signal once it has been added; however processes such as averaging and weighting different components due to prior knowledge are often combined in the nervous system to counter its influence (Faisal et al., 2008). Our task was relatively constrained and higher levels of variability clearly impaired performance. However, a freer task allowing a greater variety of motor control solutions would enable one to evaluate compensatory mechanisms against noise and uncertainty. Already work in children with dystonic cerebral palsy has suggested that when learning the novel skill of throwing a virtual ball children adjusted their motor strategy to be more tolerant to variability in timing (Chu et al., 2016).

Another important line of work which informs neuro-rehabilitation options, is that changing the sensorimotor context for patients can be helpful. Clues for this clinically may be present within sensory trick phenomena in which increased sensory feedback obtained by touching a body part (for example touching chin with hand in cervical dystonia) reduces the expression of dystonia (Patel et al., 2014). If, as our data suggests, poor performance in DYT1 dystonia is related to increases in random variability, it is likely that the motor controller has a lesser ability to extract relevant information from actual sensory feedback as most sensory streams will be polluted by this noisy stochastic component. Therefore, externally generated and augmented feedback may offer real opportunity to reduce dystonic contractions using intact feedback loops that can improve dystonic motor control. For example, in a bimanual myocontrol task in which the modified sum of the EMG amplitudes from the biceps muscles controlled the vertical position of a single red line on a computer screen, if scaled forms of vibratory feedback were given to augment sensory awareness of task-relevant information, children with dystonia were better able to suppress excessive variability (Bertucco and Sanger, 2015; Liyanagamage et al., 2017). Interestingly, occasionally, DYT1 dystonia can also improve with certain actions such as playing piano or knitting (Kojovic et al., 2012), implying that the activation of certain motor circuits reduces the severity of the dystonic manifestations.

5 Directions for future work

The limited number of core clinical movement disorders may in part reflect the limited range of responses that a motor control system can display in response to perturbation by disease. As such dystonia is considered a final common endpoint for a multitude of different etiologies as discussed. However, we also believe that disease specific kinematic signatures are likely to reside within these broad clinical classification systems. The future challenge in this field of investigation is therefore to effectively navigate between kinematic features that are disease specific yielding

insight into pathophysiology and more general patterns of change that are representative of the symptom dystonia and yet perhaps still informative for therapeutic interventions.

6 Conclusions

The pathophysiology of the dystonia's remains an enigma. The analysis of the dystonic movement itself with kinematic techniques offers real opportunity to directly probe dystonic motor control. Within such investigation we need to be mindful of the fact that the term dystonia is often used interchangeably to represent both a motor syndrome in response to a range of pathophysiological insults and also specific diseases (as in the case of the genetically homogenous DYT1 dystonia). Our work in DYT1 dystonia reveals an important role for increased motor variability and delineating the mechanisms behind how such variability is generated and why this occurs remains an important research goal. Overall, the hope is that by reverse engineering dystonic control mechanisms and utilizing intact features of the sensorimotor controller there is an optimistic future for targeted therapeutic interventions.

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