The Endophenotype and the Phenotype: Temporal Discrimination and Adult-Onset Dystonia

Michael Hutchinson, FRCP,[1,2]* Okka Kimmich, MB,[1,2] Anna Molloy, MRCPI,[1,2] Robert Whelan, PhD,[3,4] Fiona Molloy, FRCPI,[5] Tim Lynch, FRCPI,[6] Daniel G. Healy, MB, PhD,[7] Cathal Walsh, PhD,[8] Mark J. Edwards, PhD,[9] Laurie Ozelius, PhD,[10] Richard B. Reilly, PhD,[3] and Seán O'Riordan, FRCPI[1,2]

[1]Department of Neurology, St. Vincent's University Hospital, Dublin, Ireland
[2]University College Dublin, Dublin, Ireland
[3]Trinity Centre for Bioengineering, Trinity College, Dublin, Ireland
[4]Department of Psychiatry, University of Vermont, Burlington, Vermont, USA
[5]Department of Neurophysiology, Beaumont Hospital, Dublin, Ireland
[6]Department of Neurology, Mater Misericordiae University Hospital, Dublin, Ireland
[7]Department of Neurology, Beaumont Hospital, Dublin, Ireland
[8]Department of Statistics, Trinity College, Dublin, Ireland
[9]Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, United Kingdom
[10]Departments of Genetics and Genomic Sciences and Neurology, Ichan School of Medicine at Mount Sinai, New York, New York, USA

ABSTRACT: The pathogenesis and the genetic basis of adult-onset primary torsion dystonia remain poorly understood. Because of markedly reduced penetrance in this disorder, a number of endophenotypes have been proposed; many of these may be epiphenomena secondary to disease manifestation. Mediational endophenotypes represent gene expression; the study of trait (endophenotypic) rather than state (phenotypic) characteristics avoids the misattribution of secondary adaptive cerebral changes to pathogenesis. We argue that abnormal temporal discrimination is a mediational endophenotype; its use facilitates examination of the effects of age, gender, and environment on disease penetrance in adult-onset dystonia. Using abnormal temporal discrimina-

tion in unaffected first-degree relatives as a marker for gene mutation carriage may inform exome sequencing techniques in families with few affected individuals. We further hypothesize that abnormal temporal discrimination reflects dysfunction in an evolutionarily conserved subcortical-basal ganglia circuit for the detection of salient novel environmental change. The mechanisms of dysfunction in this pathway should be a focus for future research in the pathogenesis of adult-onset primary torsion dystonia. © 2013 International Parkinson and Movement Disorder Society

Key Words: focal dystonia; temporal discrimination; putamen; mediational endophenotype; phenotype

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Adult-Onset Primary Torsion Dystonia: The Problem

Adult-onset primary torsion dystonia (AOPTD) is the most common form of dystonia, expressed as various phenotypes thought to result from a combination of shared common susceptibility genes with additional individual genetic and environmental risk factors. Heterogeneity of the phenotype among affected individuals in multiplex families supports this assumption.[1,2] In families with 2 members affected by AOPTD, proband-relative pairs had different phenotypes in 46% of pairs.[3] There is also evidence that the phenotype is determined by the age of the patient at disease penetrance.[2] Segregation analyses suggest an

autosomal dominant inheritance with markedly reduced penetrance of 10% to 15%.[4–7] Therefore, most AOPTD cases appear to be sporadic and genes affecting only a few families have been identified to date.[8–10]

Endophenotypes are subclinical quantitative markers of gene expression and their use may help to elucidate the genetic basis and pathogenesis of poorly penetrant disorders. Several putative endophenotypes in AOPTD have been proposed.[11] In this work we argue that abnormal temporal discrimination threshold (TDT) is a valid endophenotype in AOPTD and indicates a distinct pathogenetic mechanism which involves a subcortical–basal ganglia circuit. The main input to this circuit, the superior colliculus, responds to multiple sensory stimuli for the detection of biologically salient environmental events. We also argue that reported cortical abnormalities in AOPTD probably represent secondary phenomena (secondary endophenotypes) rather than primary pathogenetic mechanisms of AOPTD.
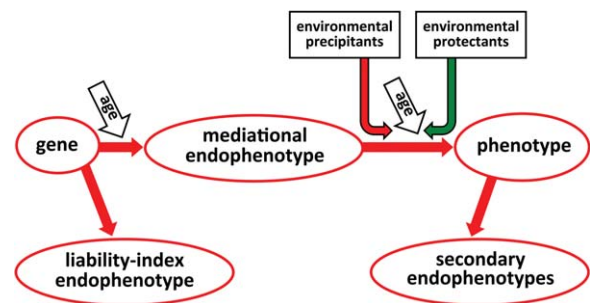
Endophenotypes: Mediational and Others

Although applied mainly in psychiatric research, the endophenotype concept is relevant to poorly penetrant forms of dystonia. The salient characteristics of an ideal endophenotype have been defined by various authors.[12–14]

The mediational endophenotype model implies that the endophenotype and the disease are both caused by a genetic disorder and that the pathway from gene to disease passes through the endophenotype; one cannot acquire the disease without first having the endophenotype.[15] A mediational endophenotype reflects disease susceptibility, is not altered by disease severity, is closer to genetic mechanisms of expression and is more penetrant than the phenotype. Mediational endophenotypes by necessity in an autosomal dominant disorder such as AOPTD, should be found, depending on penetrance, in up to 50% of unaffected first-degree relatives. Very few of the postulated endophenotypes in AOPTD fulfill this criterion.

Some Endophenotypes Are Epiphenomena

An endophenotype may be an epiphenomenon if both the disease and the endophenotype are caused by a genetic abnormality but there is no other relationship between them (the liability index model). The more common epiphenomenon occurs when the endophenotype results from disease manifestation with adaptive, compensatory, secondary cerebral changes;

FIG. 1. Diagram illustrating the interaction between genotype, a mediational endophenotype, other endophenotypes, and the phenotype. Mediational endophenotypes are closer to the genotype than the phenotype, share common pathogenetic mechanisms with the phenotype, and the pathway from gene to disease passes through the endophenotype. Secondary endophenotypes arise solely through disease manifestation. The liability-index model of an endophenotype implies that both the disease and the endophenotype are caused by the genotype but there is no other relationship between them.

this is a secondary endophenotype (Fig. 1). Mediational endophenotypes are found in non-manifesting gene carriers and represent a trait, whereas secondary endophenotypes are found only in the disease state. There has been a tendency in the last 10 years in the movement disorder literature to use the term endophenotype to describe findings on investigation that associate with the disease state and which are presumed to be pathogenetic. We argue that these are epiphenomena arising from either of these 2 mechanisms (liability index or secondary).

Trait Versus State in AOPTD

Secondary endophenotypes may include cortical changes detected by neurophysiological, imaging, and biophysical tests in various AOPTD phenotypes. For example, impaired intracortical inhibition and plasticity have been found in focal hand dystonia[16,17] and cervical dystonia,[18] but have *not* been shown to be abnormal in unaffected first-degree relatives. Treatment with botulinum toxin, in patients with upper limb dystonia, temporarily alters cortical excitability and restores intracortical inhibition by decreasing muscle spindle input 1 month after injection;[19] this, however, was not confirmed by others.[20]

Abnormal spatial discrimination has been described in focal hand dystonia[21] and cervical dystonia[22] with disorganized cortical somatotopy in focal hand dystonia.[23] Treatment with botulinum toxin temporarily improves abnormal spatial discrimination in cervical dystonia[24] and reverses the abnormal motor cortical representation of the hand in cervical dystonia,[25] whereas intensive rehabilitation normalizes cortical sensory somatopy in focal hand dystonia.[26] The improvement of these abnormalities in response to symptomatic therapies suggests that they represent secondary adaptation to disease manifestation. In

TABLE 1. A summary of the features of the mediational endophenotype, an abnormal TDT (first column), contrasted to those of the phenotype, AOPTD (second column)

Endophenotype: abnormal TDT	Phenotype: AOPTD
Closer to the gene	Further from the gene
Quantitative marker: dichotomizes subjects	Qualitative marker: diagnosis by expert opinion
Highly penetrant by 48 y of age	Poorly penetrant; age at penetrance affects phenotype
Uniform expression	Variable expression
Needed to develop phenotype	n/a
Linkage analysis possible by identification of gene carriers; endophenocopies a risk (>60 y)	Reduced penetrance, limits linkage analysis; phenocopies a risk
Not affected by environmental factors	Environmental factors involved in penetrance
Indicates pathogenetic mechanisms of disease causation	Weakly indicative of disease pathogenesis
Supported by other mediational endophenotypes	May cause "secondary endophenotypes"
A pure expression of the genotype	Confounded by secondary adaptive changes

These features are discussed in detail in the text.
TDT, temporal discrimination threshold; AOPTD, adult onset primary torsion dystonia; n/a, not applicable.

contrast, a candidate mediational endophenotype, abnormal temporal discrimination threshold, is not altered by symptomatic therapy for dystonia, including deep brain stimulation (DBS)[27] and botulinum toxin therapy.[28]

Despite recent emphasis on abnormalities of cortical function detected by various techniques as primary abnormalities in AOPTD,[29,30] we suggest that these cortical abnormalities in AOPTD probably represent epiphenomena. Secondary dystonia is not seen in patients with discrete cerebral cortical lesions and the argument that primary dystonia reflects disordered basal ganglia circuitry has been clearly stated.[31]

Trait Versus STATE in DYT1 Dystonia

The differences between trait and state measures are most easily assessed in DYT1 and DYT6 dystonia where non-manifesting carriers (NMC) can be clearly defined. Using [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET), Carbon et al.[32] and Carbon and Eidelberg[33] compared patterns of regional metabolic activity between NMC and clinically affected DYT1 and DYT6 carriers. Manifesting DYT1 and DYT6 patients showed a pattern of increased activity called the dystonia manifestation-related pattern (DYT-RP) whereas NMC of either genotype showed *reduced* DYT-RP expression. Manifesting carriers had developed abnormal cortical sensorimotor integration. Thus, by using FDG-PET, penetrance-related increased metabolic activity in the cortex (a secondary endophenotype) was distinctly different from the genotype-related effects.

In an earlier study comparing NMC and manifesting carriers of the DYT1 gene, both groups of carriers were found to have significant reduction in intracortical inhibition but the NMC participants had normal spinal reciprocal inhibition.[34] The authors noted that the cortical abnormalities in the NMC were in pathways influenced by basal ganglia output and that the additional abnormalities in the manifesting DYT1 patients may be secondary to disease manifestation affecting connected structures.

The evidence that some electrophysiological abnormalities are secondary to the movement disorder is supported by findings that dystonia patients, with various phenotypes, treated successfully with pallidal DBS, postoperatively show slowly improving markers of impaired cortical inhibition that correlate to clinical response and early response to plasticity protocols.[35] In contrast, abnormal temporal discrimination is not corrected by DBS for dystonia despite clinical improvement.[27]

TDT as a Mediational Endophenotype in AOPTD

A number of putative endophenotypes have been identified for AOPTD.[11] We and others have examined the utility of the TDT as a valid mediational endophenotype in both familial and sporadic AOPTD.[36–44] The TDT is defined as the shortest time interval in which 2 stimuli may be determined as asynchronous (normally about 30–40 ms). The TDT is regarded as abnormal if >2.5 SD above the control mean (TDT Z-score >2.5). Abnormal TDTs show autosomal dominant transmission in multiplex AOPTD families[43] and in families of sporadic AOPTD patients.[42] Unaffected obligate heterozygotes have abnormal TDTs.[43] The TDT is abnormal in more than 80% to 90% of patients with various AOPTD phenotypes, and sensitivity is highest (97%) in the most common phenotype, cervical dystonia.[44] The specificity of an abnormal TDT in various studies is 98% to 100%. There is age-related penetrance of an abnormal TDT in unaffected first-degree relatives with full penetrance by 48 years of age in women and 40%
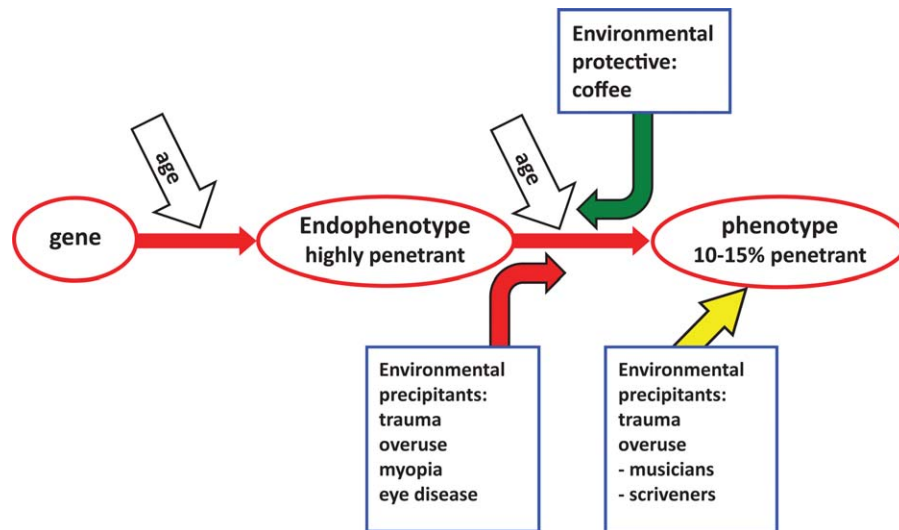
FIG. 2. The concept of the mediational endophenotype (abnormal temporal discrimination) applied to adult onset primary torsion dystonia (AOPTD) and environmental factors that affect penetrance of the phenotype. Age-related full penetrance of the endophenotype develops in unaffected first-degree female relatives by 48 years of age with 40% penetrance in male relatives.[45] The phenotype is poorly penetrant and depends on age and other environmental factors including trauma,[53] overuse (in focal hand dystonia[53] and musicians[51]), and eye disease (in blepharospasm).[52] There is evidence that coffee drinking is protective.[52] Trauma may not be an environmental risk factor for AOPTD penetrance; an increased propensity to trauma may be a result of having abnormal temporal discrimination. Whether all AOPTD is genetic is not clear: the yellow arrow suggests that there may be a mechanism whereby some environmental agents (overuse) may cause focal dystonia without preceding genetic liability.

penetrance in men.[45] Unaffected relatives with abnormal TDTs have larger putaminal volumes by voxel-based morphometry (VBM) than relatives with normal TDTs.[43] An abnormal TDT is not specific to AOPTD, having been found also in other basal ganglia disorders[46–48] and in NMC of DYT1 dystonia[38] and PINK1 Parkinsonism.[49]

The finding of abnormal TDTs in these other basal ganglia disorders may be regarded by some as a weakness in the hypothesis that abnormal temporal discrimination is a mediational endophenotype in AOPTD. However, the presence of abnormal TDTs in diseases with obviously abnormal dopamine processing supports a thesis that temporal discrimination is a marker of a disturbed basal ganglia circuit involving dopamine processing in the putamen (described in Fig. 4).

Apart from scientific curiosity, the concept an abnormal TDT as a mediational endophenotype has a number of important implications for our understanding of the pathogenesis of AOPTD.

The Mediational Endophenotype Concept as a Hypothesis Generator

Five hypotheses arise from considering abnormal temporal discrimination as a mediational endophenotype in AOPTD (Table 1).
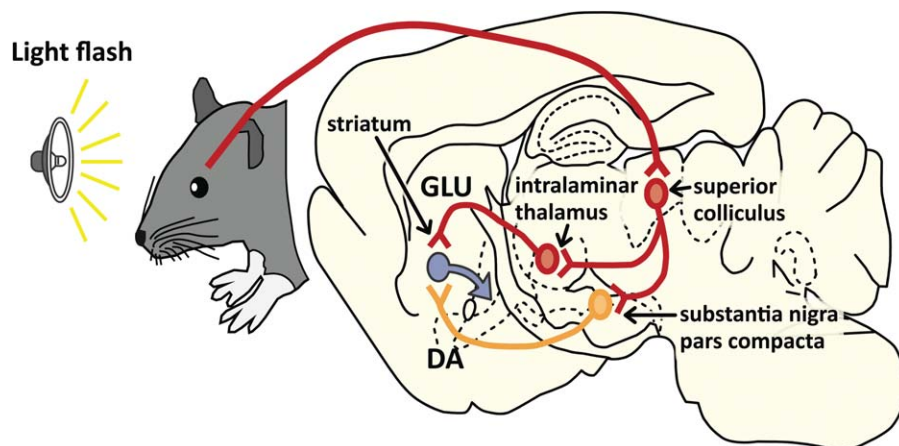
FIG. 3. The postulated input to the subcortical basal ganglia circuit involved in the detection of salient unexpected environmental change and in the temporal discrimination task (from Peter Redgrave[75] with permission). Direct retinal input to the superior colliculus affects branched projections to the intralaminar thalamic nuclei and to the substantia nigra pars compacta. Converging phasic inputs to the striatum from the thalamic intralaminar nuclei (GLU, glutamate) and substantia nigra (DA, dopamine) signal unexpected salient environmental change and affect striatal output (see Fig. 4).

Trait Versus State

An endophenotypic marker in non-manifesting gene mutation carriers is purely genotype-specific whereas a phenotypic marker may be a secondary disorder of cerebral function. The advantage of examining trait rather than state-dependent abnormalities is that the trait abnormality is linked to genetic inheritance and more probably relates to the underlying disease pathogenesis.

The Endophenotype as a Tool to Explore Environmental Factors in AOPTD

If the endophenotype, an abnormal TDT, is fully penetrant and the phenotype, AOPTD, only weakly penetrant, one might compare antecedent environmental exposures between clinically affected individuals and their similarly aged, unaffected, siblings (aged 40 years or older) who have abnormal TDTs in a matched phenotype-endophenotype study. Previous studies of environmental factors in disease expression in AOPTD have compared affected individuals with unaffected first-degree relatives[50–52] or with non-family members who have other, nondystonic, disorders.[53,54] The power and specificity of a study of environmental factors would be considerably increased by comparing affected AOPTD patients with their similarly aged, or older siblings who have abnormal TDTs (postulated to be non-manifesting gene carriers) (Fig. 2). Comparing the history of various environmental exposures, for example to peripheral trauma, in 3 groups: (1) patients with AOPTD; (2) their siblings of similar ages with normal TDTs; and (3) siblings with abnormal TDTs, may determine those environmental exposures that influence the risk of developing AOPTD.

The Endophenotype in Gene Discovery

It is likely that AOPTD is genetically heterogeneous with a number of different genetic mutations causing similar phenotypes. Informative multiplex AOPTD families are rare. Studies on multiplex families are likely to be productive using exome sequencing techniques (as has recently been demonstrated[10]). The use of a valid, reliable endophenotype in multiplex families, by indicating gene carriage in unaffected family members, might facilitate successful linkage analysis or exome sequencing.[10,55] Cosegregating single-nucleotide polymorphism variants identified in multiplex AOPTD families may be screened in other family members with and without abnormal TDT scores to validate the endophenotype. A validated TDT endophenotype could then be used in the further examination by linkage analysis of multiplex families with few affected individuals.

## The Mediational Endophenotype, Abnormal TDT, Indicates the Pathogenetic Mechanisms of AOPTD

Understanding the anatomy and physiology of normal temporal discrimination and the pathophysiology of an abnormal TDT may indicate novel pathogenic mechanisms of AOPTD. Evidence supporting the role of an abnormal TDT in the pathogenesis of AOPTD includes structural and functional abnormalities implicating the putamen and, more specifically, disordered dopamine processing.

This evidence includes:

1. Putaminal enlargement in patients with AOPTD[56,57] and musicians with task-related dystonia.[58] Unaffected first-degree relatives of AOPTD patients with abnormal TDTs also have putaminal enlargement compared to relatives with normal TDTs.[43] It is to be noted that putaminal hypertrophy seems to be associated with dysfunction (unlike in the cortex where atrophy is associated with dysfunction). For example, in musicians there is a relationship between worsening performance of key-stroke and increased putaminal size.[58] However, the relationship between AOPTD and putaminal hypertrophy has recently been questioned.[30]

2. Perceptual certainty in a temporal discrimination task is associated with putaminal activation[59]; the putamen is involved early in a temporal processing task.[60,61]

3. Reduced putaminal dopamine 2 receptor (D2R) availability is found in cranial dystonia,[62] focal hand dystonia,[63] cervical dystonia,[64] and in manifesting and NMC of both DYT1 and DYT6 dystonia.[65,66] One required experiment would be to assess D2R availability in AOPTD patients and their unaffected siblings with abnormal TDTs in comparison to their similar-age siblings with normal TDTs.

4. Abnormal temporal discrimination is found in Parkinson's disease[46,47,67,68] and is improved by L-dopa replacement but not by subthalamic nucleus DBS.[68]

Abnormal Temporal Discrimination as a Mediational Endophenotype Indicates a Disordered Subcortical-Basal Ganglia Circuit in AOPTD

The hypothesis is that normal temporal discrimination is a marker of the integrity of an alerting system to novel environmental change. Normal temporal discrimination can detect changes in the visual and tactile
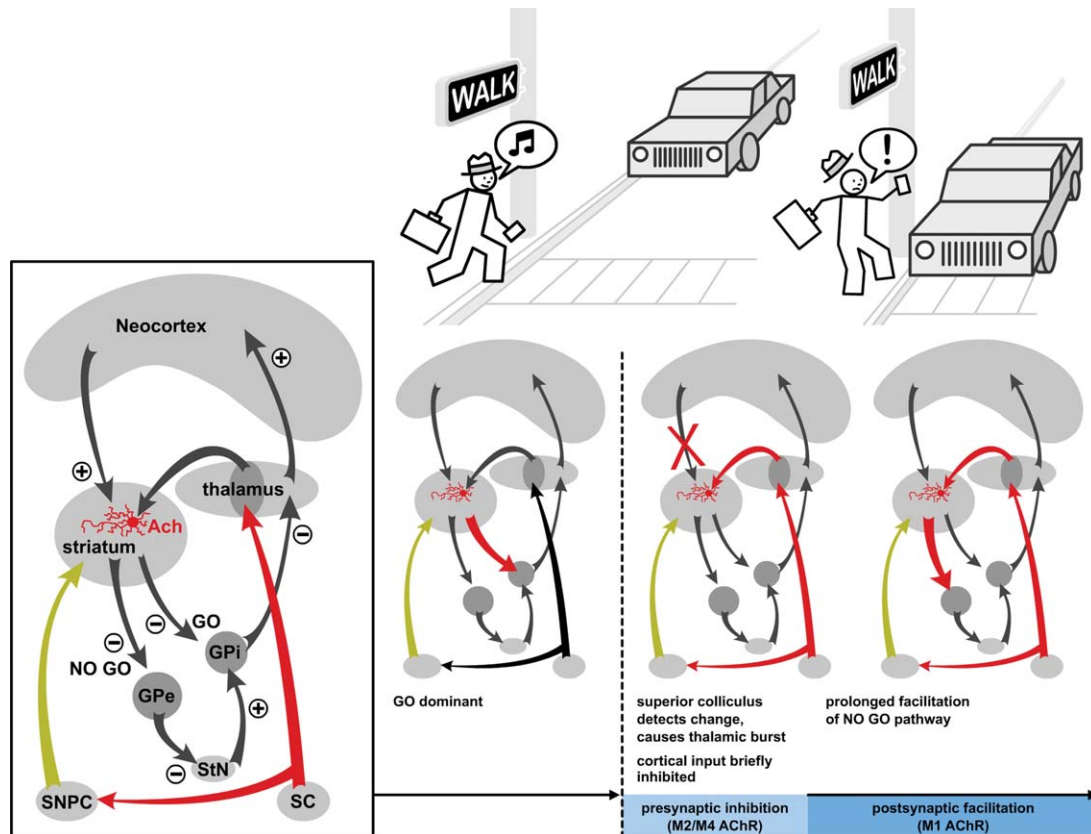
FIG. 4. The subcortical basal ganglia circuit involved in the detection of, and response to, unexpected environmental events. In response to perceived danger a stimulus from the superior colliculus (SC) to the intralaminar thalamic neurons causes a burst of firing in thalamostriatal pathway to the cholinergic interneurons. This thalamic burst elicits a burst and pause response in the striatal cholinergic interneurons. The resultant burst of acetylcholine momentarily interrupts the corticostriatal input to the medium spiny neurons of both the direct "GO" and indirect "NO-GO" pathway via activation of presynaptic M2/M4 receptors (middle right circuit cartoon). The pause allows prolonged facilitation in the indirect ("NO-GO") pathway caused by activation of postsynaptic M1 receptors on the medium spiny neurons in the indirect pathway (extreme right cartoon). Striatal dopamine release is increased both by synchronous stimulation of cholinergic interneurons and by stimulation of the substantia nigra pars compacta (SNpc) by branched afferents from the superior colliculus. Thus alerting events in the environment interrupt ongoing activity in the "GO" pathway and allow an appropriate response. We postulate it is this pathway that is involved in the temporal discrimination task. (Figure adapted from Thorn and Graybiel[85] with permission from A.M. Graybiel).

environment within a remarkably defined short interval of approximately 30 to 40 ms and may have evolutionary significance. Such an alerting mechanism would be of use in detecting prey or avoiding a predator (Fig. 3). Dopamine plays a pivotal role in motivational control and reward processing but its role in alerting organisms to novel environmental events has only recently been recognized.[69] Mid-brain dopaminergic neurons exhibit short-latency responses to biologically salient events.[70]

The Superior Colliculus: Detecting and Selecting Salient Stimuli for Reaction

The superior colliculus is a laminated structure with a superficial purely sensory layer responding to visual inputs directly from the retina. Neurons in the deeper layers respond to multisensory, visual, auditory, and tactile inputs.[71,72] There is increasing evidence that superior colliculus activity is central to the detection of unpredictable, biologically salient events that can trigger interruption of ongoing behavior, contribute to higher-order decision making, and initiate orienting responses of the head and eyes.[73]

The anatomical pathway by which salient environmental changes influence motor responses involves a subcortical basal ganglia loop.[72,74,75] The superior colliculus is the primary source of short-latency visual inputs to the dopaminergic cells of the substantia nigra pars compacta (SNpc)[76] and the intralaminar thalamic neurons (which innervate the cholinergic striatal interneurons[77]); this pathway has been demonstrated in the rat[78] and in primates.[79,80]

It has been known for some time that the main output from the intralaminar thalamic nucleus is to the cholinergic interneurons of the striatum.[81] These neurons in behaving primates respond to unexpected visual, auditory, or somatosensory stimuli with brief

short-latency firing, signaling biologically salient events unrelated to reward. Although neurologists have often regarded the interplay of dopamine and acetylcholine in the striatum as apparently antagonistic (in Parkinson's disease for example), more recent sophisticated in vitro studies have shown that synchronous stimulation of cholinergic interneurons dramatically elevates striatal dopamine release.[82,83] Also, activation of glutaminergic thalamic inputs to the striatum evokes dopamine release.[83]

Recent experimental work in animals has demonstrated that thalamic stimulation excites a burst-and-pause response in the cholinergic interneurons of the striatum. The resultant burst of acetylcholine release causes a brief decrease in corticostriatal transmission to medium spiny neurons in both the direct and indirect pathways, via activation of presynaptic M2/M4 receptors.[84] This is followed by prolonged facilitation of transmission in the indirect ("no-go"), but not the direct ("go"), pathway, caused by activation of postsynaptic M1 receptors on medium spiny neurons in the indirect pathway.[85] This provides a mechanism for cessation of ongoing activity in response to a biologically salient event and, if required, a redirection of behavior appropriate to the environmental change that has been detected.

Temporal Discrimination: A Measure of the Detection of Salient Environmental Change

In humans, the temporal discrimination threshold is a measure of the efficacy of detection of salient environmental change and is a function of the collicular-thalamic-putaminal-pallidal-nigral loop described in Figure 4. Undoubtedly temporal discrimination is also later processed by cortical areas,[60] but the weight of evidence adduced above indicates that the TDT task in our experimental paradigm is largely a function of this subcortical basal ganglia pathway.

Predators and prey are unlikely concerns for the urbanized human. However, accurate detection of looming objects and estimation of time to collision are important functions for safety in our daily lives, whether as cyclists, pedestrians, or drivers (Fig. 4). In an fMRI study in humans, whereas timing computations for collision events were functions of the anterior insula, the *detection* of the looming stimulus (opposed to a receding stimulus) was associated with activation of both superior colliculi.[86] It is possible that the association of peripheral trauma with later development of AOPTD[53] may not be causal and that individuals with prolonged temporal discrimination also have reduced ability to detect in a short time a salient environmental stimulus and thus are less able to avoid trauma.

Conclusion

Mediational endophenotypes may be powerful tools to advance our understanding of the pathogenesis of AOPTD. Clearly, the ultimate validation of abnormal temporal discrimination as a mediational endophenotype of AOPTD will depend on gene discovery, but the accumulating indirect evidence is compelling. Future research on the pathogenesis of AOPTD should be focused on the disrupted subcortical–basal ganglia pathway implicated by abnormal temporal discrimination. ∎

References

1. Brancati F, Defazio G, Caputo V, et al. Novel Italian family supports clinical and genetic heterogeneity of primary adult-onset torsion dystonia. Mov Disord 2002;17:392–397.
2. O'Riordan S, Raymond D, Lynch T, et al. Age at onset as a factor in determining the phenotype of primary torsion dystonia. Neurology 2004;63:1423–1426.
3. Defazio G, Berardelli A, Hallett M. Do primary adult-onset focal dystonias share aetiological factors? Brain 2007;130:1183–1193.
4. Waddy HM, Fletcher NA, Harding AE, Marsden CD. A genetic study of idiopathic focal dystonias. Ann Neurol 1991;29:320–324.
5. Stojanović M, Cvetković D, Kostić VS. A genetic study of idiopathic focal dystonias. J Neurol 1995;242:508–511.
6. Leube B, Kessler KR, Goecke T, Auburger G, Benecke R. Frequency of familial inheritance among 488 index patients with idiopathic focal dystonia and clinical variability in a large family. Mov Disord 1997;12:1000–1006.
7. Groen JL, Kallen MC, van de Warrenburg BP, et al. Phenotypes and genetic architecture of focal primary torsion dystonia. J Neurol Neurosurg Psychiatry 2012;83:1006–1011.
8. Leube B, Rudnicki D, Ratzlaff T, Kessler KR, Benecke R, Auburger G. Idiopathic torsion dystonia: assignment of a gene to chromosome 18p in a German family with adult onset, autosomal dominant inheritance and purely focal distribution. Hum Mol Genet 1996;5:1673–1677.
9. Xiao J, Zhao Y, Bastian RW, et al. Novel THAP1 sequence variants in primary dystonia. Neurology 2010;74:229–238.
10. Fuchs T, Saunders-Pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2012;45:88–92.
11. Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. Brain 2012;135:1668–1681.
12. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636–645.
13. Preston GA, Weinberger DR. Intermediate phenotypes in schizophrenia: a selective review. Dialogues Clin Neurosci 2005;7:165–179.
14. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. Annu Rev Clin Psychol 2006;2:267–290.
15. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. Mol Psychiatry 2010;15:789–797.
16. Tamura Y, Matsuhashi M, Lin P, et al. Impaired intracortical inhibition in the primary somatosensory cortex in focal hand dystonia. Mov Disord 2008;23:558–565.
17. Tamura Y, Ueki Y, Lin P, et al. Disordered plasticity in the primary somatosensory cortex in focal hand dystonia. Brain 2009;132:749–755.
18. Kanovský P, Bares M, Streitová H, Klajblová H, Daniel P, Rektor I. Abnormalities of cortical excitability and cortical inhibition in

cervical dystonia: evidence from somatosensory evoked potentials and paired transcranial magnetic stimulation recordings. J Neurol 2003;250:42–50.

19. Gilio F, Curra A, Lorenzano C, Modugno N, Manfredi M, Berardelli A. Effects of botulinum toxin type A on intracortical inhibition in patients with dystonia. Ann Neurol 2000;48:20–26.

20. Boroojerdi B, Cohen LG, Hallett M. Effects of botulinum toxin on motor system excitability in patients with writer's cramp. Neurology 2003;61:1546–1550.

21. Molloy FM, Carr TD, Zeuner KE, Dambrosia JM, Hallett M. Abnormalities of spatial discrimination in focal and generalized dystonia. Brain 2003;126:2175–2182.

22. O'Dwyer JP, O'Riordan S, Saunders-Pullman R, et al. Sensory abnormalities in unaffected relatives in familial adult-onset dystonia. Neurology 2005;65:938–940.

23. Meunier S, Garnero L, Ducorps A, et al. Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. Ann Neurol 2001;50:521–527.

24. Walsh R, Hutchinson M. Molding the sensory cortex: spatial acuity improves after botulinum toxin treatment for cervical dystonia. Mov Disord 2007;22:2443–2446.

25. Thickbroom GW, Byrnes ML, Stell R, Mastaglia FL. Reversible reorganization of the motor cortical representation of the hand in cervical dystonia. Mov Disord 2003;18:395–402.

26. Bleton JP, Vidailhet M, Bourdain F, et al. Somatosensory cortical remodeling after rehabilitation and clinical benefit of in writer's cramp. J Neurol Neurosurg Psychiatry 2011;82:574–577.

27. Sadnicka A, Kimmich O, Pisarek C, et al. Pallidal stimulation for cervical dystonia does not correct abnormal temporal discrimination. Mov Disord 2013;28:1874–1876.

28. Scontrini A, Conte A, Fabbrini G, Colosimo C, Di Stasio F, Ferrazzano G, et al. Somatosensory temporal discrimination tested in patients receiving botulinum toxin injection for cervical dystonia. Mov Disord 2011;26:742–746.

29. Delnooz CC, Helmich RC, Toni I, van de Warrenburg BP. Reduced parietal connectivity with a premotor writing area in writer's cramp. Mov Disord 2012;27:1425–1431.

30. Martino D, Di Giorgio A, D'Ambrosio E, Popolizio T, Macerollo A, Livrea P, Bertolino A, Defazio G. Cortical gray matter changes in primary blepharospasm: a voxel-based morphometry study. Mov Disord 2011;26:1907–1912.

31. Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. Brain 1998;121:1195–1212.

32. Carbon M, Su S, Dhawan V, Raymond D, Bressman S, Eidelberg D. Regional metabolism in primary torsion dystonia: effects of penetrance and genotype. Neurology 2004;62:1384–1390.

33. Carbon M, Eidelberg D. Abnormal structure-function relationships in hereditary dystonia. Neuroscience 2009;164:220–229.

34. Edwards MJ, Huang YZ, Wood NW, Rothwell JC, Bhatia KP. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. Brain 2003;126:2074–2080.

35. Ruge D, Tisch S, Hariz MI, Zrinzo L, Bhatia KP, Quinn NP, et al. Deep brain stimulation effects in dystonia: time course of electrophysiological changes in early treatment. Mov Disord 2011;26:1913–1921.

36. Sanger TD, Tarsy D, Pascual-Leone A. Abnormalities of spatial and temporal sensory discrimination in writer's cramp. Mov Disord 2001;16:94–99.

37. Fiorio M, Tinazzi M, Bertolasi L, Aglioti SM. Temporal processing of visuotactile and tactile stimuli in writer's cramp. Ann Neurol 2003;53:630–635.

38. Fiorio M, Gambarin M, Valente EM, Liberini P, Loi M, Cossu G, et al. Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia? Brain 2007;130:134–142.

39. Fiorio M, Tinazzi M, Scontrini A, Stanzani C, Gambarin M, Fiaschi A, et al. Tactile temporal discrimination in patients with blepharospasm. J Neurol Neurosurg Psychiatry 2008;79:796–798.

40. Scontrini A, Conte A, Defazio G, Fiorio M, Fabbrini G, Suppa A, et al. Somatosensory temporal discrimination in patients with pri-

mary focal dystonia. J Neurol Neurosurg Psychiatry 2009;80:1315–1319.

41. Bradley D, Whelan R, Walsh R, O'Dwyer J, Reilly R, Hutchinson S, et al. Comparing endophenotypes in adult-onset primary torsion dystonia. Mov Disord 2010;25:84–90.

42. Kimmich O, Bradley D, Whelan R, Mulrooney N, Reilly RB, Hutchinson S, et al. Sporadic adult onset primary torsion dystonia is a genetic disorder by the temporal discrimination test. Brain 2011;134:2656–2663.

43. Bradley D, Whelan R, Walsh R, Reilly RB, Hutchinson S, Molloy F, et al. Temporal Discrimination Threshold: VBM evidence for an endophenotype in adult onset primary torsion dystonia. Brain 2009;132:2327–2335.

44. Bradley D, Whelan R, Kimmich O, O'Riordan S, Mulrooney N, Brady P, et al. Temporal discrimination thresholds in adult-onset primary torsion dystonia: an analysis by task type and by dystonia phenotype. J Neurol 2012;259:77–82.

45. Kimmich O, Molloy A, Whelan R, Williams L, Bradley D, Balsters J, et al. Temporal discrimination, a cervical dystonia endophenotype : penetrance and functional correlates. 2013 (in preparation).

46. Artieda J, Pastor MA, Lacruz F, Obeso JA. Temporal discrimination is abnormal in Parkinson's disease. Brain 1992;115:199–210.

47. Lee MS, Kim HS, Lyoo CH. "Off" gait freezing and temporal discrimination threshold in patients with Parkinson disease. Neurology 2005;64:670–674.

48. Lyoo CH, Lee SY, Song TJ, Lee MS. Abnormal temporal discrimination threshold in patients with multiple system atrophy. Mov Disord 2007;22:556–559.

49. Fiorio M, Valente EM, Gambarin M, Bentivoglio AR, Ialongo T, Albanese A, et al. Subclinical sensory abnormalities in unaffected PINK1 heterozygotes. J Neurol 2008;255:1372–1377.

50. Schweinfurth JM, Billante M, Courey MS. Risk factors and demographics in patients with spasmodic dysphonia. Laryngoscope 2002;112:220–223.

51. Schmidt A, Jabusch HC, Altenmüller E, Hagenah J, Brüggemann N, Lohmann K, et al. Etiology of musician's dystonia: familial or environmental? Neurology 2009;72:1248–1254.

52. Defazio G, Abbruzzese G, Aniello MS, Bloise M, Crisci C, Eleopra R, et al. Environmental risk factors and clinical phenotype in familial and sporadic primary blepharospasm. Neurology 2011;77:631–637.

53. Roze E, Soumaré A, Pironneau I, Sangla S, de Cock VC, Teixeira A, et al. Case-control study of writer's cramp. Brain 2009;132:756–764.

54. Martino D, Defazio G, Abbruzzese G, Girlanda P, Tinazzi M, Fabbrini G, et al. Head trauma in primary cranial dystonias: a multicentre case-control study. J Neurol Neurosurg Psychiatry 2007;78:260–263.

55. Ku CS, Cooper DN, Polychronakos C, Naidoo N, Wu M, Soong R. Exome sequencing: dual role as a discovery and diagnostic tool. Ann Neurol 2012;71:5–14.

56. Etgen T, Mühlau M, Gaser C, Sander D. Bilateral grey-matter increase in the putamen in primary blepharospasm. J Neurol Neurosurg Psychiatry 2006;77:1017–1020.

57. Draganski B, Schneider SA, Fiorio M, Klöppel S, Gambarin M, Tinazzi M, et al. Genotype-phenotype interactions in primary dystonias revealed by differential changes in brain structure. Neuroimage 2009;47:1141–1147.

58. Granert O, Peller M, Jabusch HC, Altenmuller E, Siebner HR. Sensorimotor skills and focal dystonia are linked to putaminal grey-matter volume in pianists. J Neurol Neurosurg Psychiatry 2011;82:1225–1231.

59. Pastor MA, Macaluso E, Day BL, Frackowiak RSJ. Putaminal activity is related to perceptual certainty. Neuroimage 2008;41:123–129.

60. Rao SM, Mayer AR, Harrington DL. The evolution of brain activation during temporal processing. Nat Neurosci 2001;4:317–323.

61. Nenadic I, Gaser C, Volz HP, Rammsayer T, Häger F, Sauer H. Processing of temporal information and the basal ganglia: new evidence from fMRI. Exp Brain Res 2003;148:238–246.

62. Perlmutter JS, Stambuk MK, Markham J, Black KJ, McGee-Minnich L, Jankovic J et al. Decreased [18F]spiperone binding in

putamen in idiopathic focal dystonia. J Neurosci 1997;17:843–850.

63. Horstink CA, Praamstra P, Horstink MW, Berger HJ, Booij J, Van Royen EA. Low striatal D2 receptor binding as assessed by [123I]IBZ SPECT in patients with writer's cramp. J Neurol Neurosurg Psychiatry 1997;62:672–673.

64. Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brücke T. Imaging of the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using 123I epidepride and 123I beta-CIT. Mov Disord 1998;13:319–323.

65. Carbon M, Niethammer M, Peng S, Raymond D, Dhawan V, Chaly T, et al. Abnormal striatal and thalamic dopamine neurotransmission: Genotype-related features of dystonia. Neurology 2009;72:2097–2103.

66. Asanuma K, Ma Y, Okulski J, Dhawan V, Chaly T, Carbon M, et al. Decreased striatal D2 receptor binding in nonmanifesting carriers of the DYT1 dystonia mutation. Neurology 2005;64:347–349.

67. Malapani C, Rakitin B, Levy R, Meck WH, Deweer B, Dubois B, Gibbon J. Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction. J Cogn Neurosci. 1998;10:316–331.

68. Conte A, Modugno N, Lena F, Dispenza S, Gandolfi B, Iezzi E, et al. Subthalamic nucleus stimulation and somatosensory temporal discrimination in Parkinson's disease. Brain 2010;133:2656–2663.

69. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 2010;68:815–834.

70. Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1–27.

71. Favaro PDN, Gouvea TS, DeOliveira SR, Vautrelle N, Redgrave P, Comoli E. The influence of vibrissal somatosensory processing in rat superior colliculus on prey capture. Neuroscience 2011;176:318–327.

72. Redgrave P, Coizet V, Comoli E, McHaffie JG, Leriche M, Vautrelle N, et al. Interactions between the midbrain superior colliculus and the basal ganglia. Front Neuroanat 2010;4:132.

73. Felsen G, Mainen ZF. Midbrain contributions to sensorimotor decision making. J Neurophysiol. 2012;108:135–147.

74. McHaffie JG, Stanford TR, Stein BE, Coizet V, Redgrave P. Subcortical loops through the basal ganglia. Trends Neurosci 2005;28:401–407.

75. Redgrave P, Vautrelle N, Reynolds JN. Functional properties of the basal ganglia's re-entrant loop architecture: selection and reinforcement. Neuroscience 2011;198:138–151.

76. Dommett E, Coizet V, Blaha CD, Martindale J, Lefebvre V, Walton N, et al. How visual stimuli activate dopaminergic neurons at short latency. Science 2005;307:1476–1479.

77. Coizet V, Overton PG, Redgrave P. Collateralization of the tecto-nigral projection with other major output pathways of superior colliculus in the rat. J Comp Neurol 2007;500:1034–1049.

78. Comoli E, Coizet V, Boyes J, Bolam JP, Canteras NS, Quirk RH, et al. A direct projection from superior colliculus to substantia nigra for detecting salient visual events. Nat Neurosci. 2003;6:974–980.

79. Lovejoy LP, Krauzlis RJ. Inactivation of primate superior colliculus impairs covert selection of signals for perceptual judgments. Nat Neurosci 2010;13:261–266.

80. May PJ, McHaffie JG, Stanford TR, Jiang H, Costello MG, Coizet V, et al. Tectonigral projections in the primate: a pathway for pre-attentive sensory input to midbrain dopaminergic neurons. Eur J Neurosci 2009;29:575–587.

81. Matsumoto N, Minamimoto T, Graybiel AM, Kimura M. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviourally significant sensory events. J Neurophysiol. 2001;85:960–976.

82. Threlfell S, Lalic T, Platt NJ, Jenngs KA, Deisseroth K, Cragg SJ. Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. Neuron 2012;75:58–64.

83. Surmeier DJ, Graybiel AM. A feud that wasn't: acetylcholine evokes dopamine release in the striatum. Neuron 2012;75:1–3.

84. Ding JB, Guzman JN, Peterson JD, Goldberg JA, Surmeier DJ. Thalamic gating of corticostriatal signaling by cholinergic interneurons. Neuron 2010 67, 294–307.

85. Thorn CA, Graybiel AM. Pausing to regroup: thalamic gating of cortico-basal ganglia networks. Neuron 2010;67:175–178.

86. Billington J, Wilkie RM, Field DT, Wann JP. Neural processing of imminent collision in humans. Proc Biol Sci 2011;278:1476–1481.