Cortical Silent Period

Subjects: Biology

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The so-called cortical silent period (CSP) refers to the temporary interruption of electromyographic signal from a muscle following a motor-evoked potential (MEP) triggered by transcranial magnetic stimulation (TMS) over the primary motor cortex (M1). The neurophysiological origins of the CSP are debated. Previous evidence suggests that both spinal and cortical mechanisms may account for the duration of the CSP. However, contextual factors such as cortical fatigue, experimental procedures, attentional load, as well as neuropathology can also influence the CSP duration. The present paper summarizes the most relevant evidence on the mechanisms underlying the duration of the CSP, with a particular focus on the central role of the basal ganglia in the “direct” (excitatory), “indirect” (inhibitory), and “hyperdirect” cortico-subcortical pathways to manage cortical motor inhibition. We propose new methods of interpretation of the CSP related, at least partially, to the inhibitory hyperdirect and indirect pathways in the basal ganglia. This view may help to explain the respective shortening and lengthening of the CSP in various neurological disorders.

hyperdirect pathway | neurological disorders | cortical inhibition | basal ganglia

1. Introduction

Performing a movement involves more than just trains of muscular activations. A complex and finely tuned interplay between muscle excitation and inhibition is essential even for very simple movements. One of the most direct marks of motor inhibition, typically measured through transcranial magnetic stimulation (TMS), is the cortical silent period (CSP) [1][2]. The CSP is measured through electromyographic signal recording (EMG) on a target muscle and refers to the period of EMG silence following the elicitation of a motor-evoked potential (MEP) through a single TMS pulse delivered over the contralateral primary motor cortex (M1). Using electrical stimulation, pioneering animal electrophysiology documented the existence of CSP, indicating that excitability of cortical neurons can be reduced after brief and strong stimulation [3][4] and that inhibition lasts for 150–300 ms [5][6]. Similar results have been obtained in human subjects, showing that electrical stimulation of the cerebral cortex through the scalp can elicit CSPs [7], as well as transient functional deficits [8][9]. In parallel with improved comfort for participants [10], the introduction of TMS instead of electrical stimulation to study the characteristics of the CSP allowed the implementation of non-invasive, painless, and more spatiotemporally precise experimental protocols. For instance, one of the most established protocols in the study of cortico-spinal excitability is based on the measurement of single CSPs following a well-controlled MEP elicited by a supra-threshold single-pulse TMS delivered on M1. For both electrical stimulation and TMS, the effects of cortical stimulation on the CSP can be assessed through EMG (see Figure 1B). Nevertheless, despite the largely established reproducibility of the CSP as a direct effect of TMS-induced MEPs and its commonly accepted reliability as a measure of neural inhibition, the neurophysiological

origins of the CSP are still under debate. Revealing such origins may boost the understanding of the alterations of the CSP as often observed in several neurological diseases [11][12], possibly linked to physiological or anatomical dysfunctions at the level of the basal ganglia.

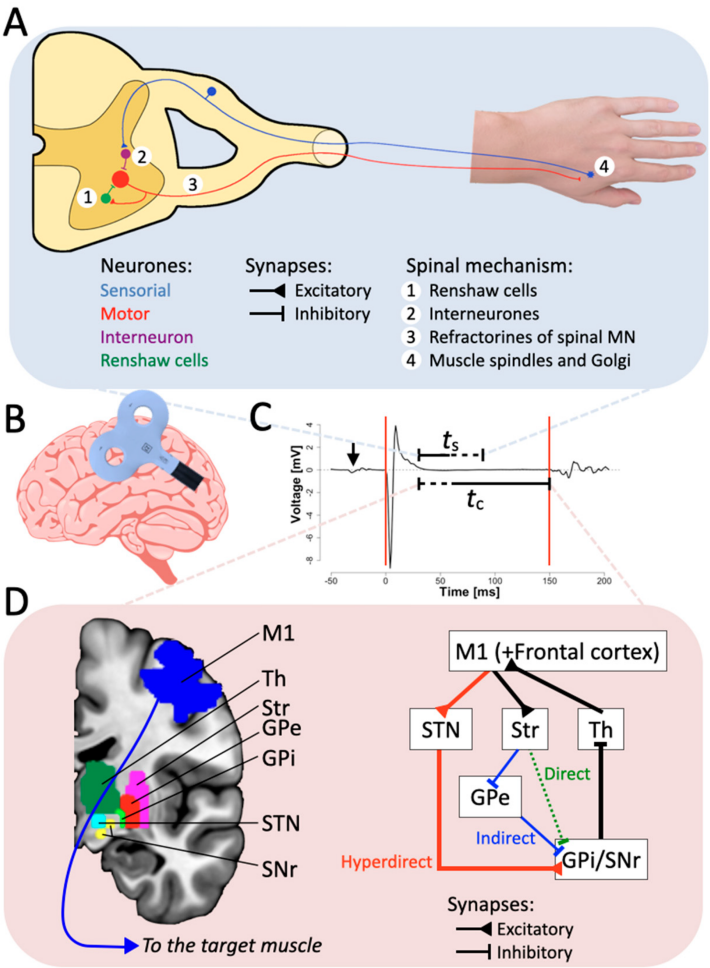

Figure 1. The inhibitory hyperdirect pathway contributes to the CSP duration. (**A**) Schematic representation of the spinal components of the CSP. Excitation of M1 through single TMS pulse reaches spinal interneuronal circuits, which in turn excite hand muscles. The four spinal mechanisms presented in the scheme contribute only to the first 50 ms of the CSP. (**B**) Schematic representation of the TMS coil stimulation in M1. (**C**) Example of an MEP. The red lines represent the usual limit defined for the CSP. "t_s" and "t_c" stand for the duration elicited by the spinal and the cortical part, respectively, and the arrow represents the TMS pulse artifact. (**D**) Simplified schematic diagram of the CBGTC loop, at least partially accounting for the later part of the CSP. Abbreviations: Str: striatum; STN: subthalamic nucleus; GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; SNr: substantia nigra pars reticulata; Th: thalamus.

2. Neural Mechanisms of CSP

2.1. Basal Ganglia Involvement in Motor Control and CSP

The basal ganglia interact with different cortical areas, with M1 as the principal output target [13]. Different circuits exist between cortical areas and basal ganglia, each having specific functions. The signals originating in the cortex arrive to the thalamus, which then returns processed signal to motor areas [11][14]. Traditionally, two major neural pathways have been described, the “direct” and the “indirect” pathways [15], as parts of the CBGTC loop [16]. As presented in a simplified schematic way in Figure 1, the direct and indirect pathways have opposite effects. In the direct pathway, excitatory signals from M1 are sent to a specific sub-area of the striatum. The neurons receiving these signals are inhibitory and send inhibitory projections to the internal part of the globus pallidus and to the substantia nigra pars reticulata. Being inhibited, the neurons in the globus pallidus/substantia nigra do not inhibit the thalamus, which in return activates the cortex. Such a direct pathway mainly leads to the activation of M1. In the indirect pathway, excitatory signals from M1 are sent to other specific sub-areas of the striatum again. The neurons receiving these signals are inhibitory and send inhibitory projections to the external part of the globus pallidus, which is inhibited and then does not activate inhibitory projections to the internal part of the globus pallidus/substantia nigra. Thus, the globus pallidus/substantia nigra is disinhibited and, in turn, can inhibit the thalamus through GABA inhibitory projections [17]. The inhibited thalamus does not activate in return the cortex. Such an indirect pathway mainly leads to inhibition of the motor cortices. In this context, there is no clear evidence that TMS over M1 activates either pathway. The neuronal excitation resulting from the TMS-associated rapid discharge of the magnetic field could potentially activate both pathways, but the result of such activation would not lead to a clear inhibition of M1. Preliminary experiments with monkeys and rats have enlightened the involvement of the subthalamic nucleus excitation on the globus pallidus and with motor control [18][19]. Furthermore, Nambu et al. [20] presented the functional significance of the “hyperdirect” pathway for motor control. Such a hyperdirect pathway bypasses the striatum involved in the direct and indirect pathways but converges in the internal part of the globus pallidus [21]. The hyperdirect pathway has a critical role in the CBGTC loop for the development of mature inhibition [22][23], is non-selective [24], and is associated with successful reactive inhibition [25]. Excitatory projections from motor areas arrive in the subthalamic nucleus, the activation of which leads to excitatory projections to the globus pallidus/substantia nigra. Activated as in the indirect pathway, the globus pallidus/substantia nigra send inhibitory projections to the thalamus, leading to suppression of thalamo-cortical output. In their model, Nambu et al. [20] propose that the hyperdirect pathway is the first circuit activated, before direct and indirect, when a voluntary movement is prepared and might play a role with the indirect pathway for inhibition of irrelevant motor programs. Accordingly, it has also been proposed that the hyperdirect pathway is a way to block rapidly a “Go” process [26][27][28], possibly in coordination with the inhibitory indirect pathway [29].

Based on this evidence, we propose that the cortical compounds of the CSP are due to the propagation of the activation signal from the TMS pulse in M1 to the CBGTC loop. In response to the strong and abrupt activation in M1, the hyperdirect pathway would generate a substantial inhibition in the thalamus. Possibly in coordination with the indirect pathway, the inhibition generated in the thalamus would be responsible for the late aspects of the CSP, at least. Such a role of the hyperdirect pathway might also be limited to high-intensity TMS pulse, as low intensity TMS pulses are more sensible to instruction or voluntary control [30]. Since the hyperdirect pathway is a faster response to motor command in the CBGTC loop with respect to the other two pathways, and the main purpose of the hyperdirect pathway is inhibition, it seems reasonable that it can contribute to the inhibition post TMS-pulse

excitation. The duration of the inhibition generated would be coherent with the inhibitory GABAergic neurotransmitter present in globus pallidus/substantia nigra stimulated after the activation of the subthalamic nucleus. Graphical representations of the spinal and cortical physiological contributions to the CSP are depicted in Figure 1.

At the cortico-subcortical level, we took into account the CBGTC loop connecting M1 and basal ganglia only in the same, ipsilateral hemisphere. However, several experiments demonstrate the influence of the contralateral hemisphere on the CSP. First, an elongation of the CSP is observed with subjects without transcallosal projections [31]. The role of the basal ganglia in transcallosal communication for M1 inhibition is not set, as deep brain stimulation of the internal globus pallidus, leading to activation of the corticospinal neurons via the internal capsule, does not lead to motor effects [32]. Further studies have to investigate the interplay between the basal ganglia and transcallosal effects on the CSP in order to understand better the role of the corpus callosum in visuomotor coordination.

2.2. Hyperdirect Pathway and Motor Neurological Disorders Influencing CSP

Animal research showed that Parkinson's disease is linked to a weakening of cortico-subthalamic connections, probably due to lower dopamine activity [33], confirming the importance of the hyperdirect pathway and dopamine distribution in the onset of Parkinson's disease. It is likely that the beneficial effects of dopamine intake on the CSP (elongation) counterbalancing the deficits due to Parkinson's disease (shortening CSP) could derive from neural dynamics occurring in the subthalamic nucleus [34]. It has been shown that electrical stimulation of the ventral part of the subthalamic nucleus can stabilize the symptoms of Parkinson's disease [35], probably stimulating dopamine release, and thus indirectly elongating the CSP. This is even less surprising as the ventral part of the subthalamic nucleus accounts for arm and hand control [36], and as most CSP determination for Parkinson's disease patients is conducted for the muscle of this region. However, broader generalizations of these findings have to be taken with caution. Even if deep brain stimulation of the subthalamic nucleus is a common treatment against Parkinson's disease [37][38], subthalamic nucleus stimulation alone does not affect the duration of the CSP and therefore the smoothness of motor execution [39]. This support the idea that the inhibition generating the CSP should originate in cortical areas, projecting then to the subthalamic nucleus. Unlike Parkinson's disease, for Huntington's disease the role of the subthalamic nucleus is debated. Schroll et al. [40] do not present results showing that Huntington's disease is due to the lesion of the subthalamic nucleus or dysfunction in dopamine circuitry. At the same time, a study on mice with hypo-functioning hyperdirect pathway presents hyperkinesic symptoms specific to Huntington's disease [41]. The neurological dysfunction of Huntington's disease are often re-evaluated [17], and the hyperdirect pathway might still be relevant in the understanding of the disease and the related effects observed on the CSP. For dystonia, it is worth noting that dystonic symptoms might result from maladaptive neuroplasticity in thalamo-basal circuits [42], which would provide already "distorted" signals to the cortex. This could be reflected in unbalanced exchanges between the hyperdirect and indirect pathways, which may explain the development of dystonic behaviors [43][44][45] in parallel with a hyperfunctional direct pathway [46]. Finally, acute ischemic stroke leading to hemiballism-hemichorea, a movement disorder characterized by possible violent involuntary movement, has been shown to be associated with lesion in the subthalamic nucleus and the hyperdirect pathway [47].

In sum, the TMS pulse over M1 could lead first to activation of the inhibitory hyperdirect pathway in the CBGTC loop. The CSP observed after an MEP seems to be the consequence of the inhibition due to first the hyperdirect pathway and then the inhibitory indirect pathway. This hypothesis is reinforced by evidence showing pathological duration of the CSP in motor neurological disorders associated with the CBGTC loop.

3. Conclusions

We put emphasis on the anatomo-functional origins of the CSP. In our view, the CSP is determined by both spinal and cortico-subcortical mechanisms. The spinal components account for up to the first 150 ms of the CSP. Then, despite spinal inhibition, cortical mechanisms also influence the CSP, as a mark of M1 inhibition, mediated by GABAergic neurons after an important cortical activation eliciting MEPs. The role of this inhibition is to prevent unwanted movements from occurring. Behavioral and cognitive factors can influence the CSP duration, as well as motor and non-motor neurological disorders. Many of these disorders present anomalies in the basal ganglia, suggesting a central role of this region in determining the characteristics of the CSP. Given that (i) motor output is mediated by the CBGTC loop and (ii) the hyperdirect pathway in the CBGTC loop has important interactions with the indirect pathway for motor inhibition, we propose that the later part of the CSP is mainly influenced by the inhibition induced by the interactions of hyperdirect and indirect pathways crossing at the level of the basal ganglia. A better comprehension of a multifaceted origin of the CSP might lead to better understanding of the physiopathology of motor and non-motor neurological disorders.

References

1. Hupfeld, K.E.; Swanson, C.W.; Fling, B.W.; Seidler, R.D. TMS-Induced Silent Periods: A Review of Methods and Call for Consistency. J. Neurosci. Methods 2020, 346, 108950.
2. Cacchio, A.; Cimini, N.; Alosi, P.; Santilli, V.; Marrelli, A. Reliability of Transcranial Magnetic Stimulation-Related Measurements of Tibialis Anterior Muscle in Healthy Subjects. Clin. Neurophysiol. 2009, 120, 414–419.
3. Adrian, E.D.; Moruzzi, G. Impulses in the Pyramidal Tract. J. Physiol. 1939, 97, 153–199.
4. Krnjević, K.; Randić, M.; Straughan, D.W. Cortical Inhibition. Nature 1964, 201, 1294–1296.
5. Krnjević, K.; Randić, M.; Straughan, D.W. An Inhibitory Process in the Cerebral Cortex. J. Physiol. 1966, 184, 16–48.
6. Cantello, R.; Gianelli, M.; Civardi, C.; Mutani, R. Magnetic Brain Stimulation: The Silent Period after the Motor Evoked Potential. Neurology 1992, 42, 1951.
7. Marsden, C.D.; Merton, P.A.; Morton, H.B. Direct Electrical Stimulation of Corticospinal Pathways through the Intact Scalp in Human Subjects. Adv. Neurol. 1983, 39, 387–391.

8. De Benedictis, A.; Sarubbo, S.; Duffau, H. Subcortical Surgical Anatomy of the Lateral Frontal Region: Human White Matter Dissection and Correlations with Functional Insights Provided by Intraoperative Direct Brain Stimulation. J. Neurosurg. 2012, 117, 1053–1069.
9. Montemurro, N.; Herbet, G.; Duffau, H. Right Cortical and Axonal Structures Eliciting Ocular Deviation during Electrical Stimulation Mapping in Awake Patients. Brain Topogr. 2016, 29, 561–571.
10. Calancie, B.; Nordin, M.; Wallin, U.; Hagbarth, K.E. Motor-Unit Responses in Human Wrist Flexor and Extensor Muscles to Transcranial Cortical Stimuli. J. Neurophysiol. 1987, 58, 1168–1185.
11. DeLong, M.R.; Wichmann, T. Circuits and Circuit Disorders of the Basal Ganglia. Arch. Neurol. 2007, 64, 20.
12. Farzan, F.; Barr, M.S.; Hoppenbrouwers, S.S.; Fitzgerald, P.B.; Chen, R.; Pascual-Leone, A.; Daskalakis, Z.J. The EEG Correlates of the TMS-Induced EMG Silent Period in Humans. NeuroImage 2013, 83, 120–134.
13. Alexander, G.E.; Crutcher, M.D. Functional Architecture of Basal Ganglia Circuits: Neural Substrates of Parallel Processing. Trends Neurosci. 1990, 13, 266–271.
14. DeLong, M.R.; Georgopoulos, A.P. Motor Functions of the Basal Ganglia. Compr. Physiol. 2011, 1017–1061.
15. Smith, Y.; Bevan, M.; Shink, E.; Bolam, J.P. Microcircuitry of the Direct and Indirect Pathways of the Basal Ganglia. Neuroscience 1998, 86, 353–387.
16. Parent, A.; Hazrati, L.-N. Functional Anatomy of the Basal Ganglia. I. The Cortico-Basal Ganglia-Thalamo-Cortical Loop. Brain Res. Rev. 1995, 20, 91–127.
17. Waldvogel, H.J.; Billinton, A.; White, J.H.; Emson, P.C.; Faull, R.L.M. Comparative Cellular Distribution of GABAA and GABAB Receptors in the Human Basal Ganglia: Immunohistochemical Colocalization of the ?1 Subunit of the GABAA Receptor, and the GABABR1 and GABABR2 Receptor Subunits. J. Comp. Neurol. 2004, 470, 339–356.
18. Kita, H.; Kita, S.T. The Morphology of Globus Pallidus Projection Neurons in the Rat: An Intracellular Staining Study. Brain Res. 1994, 636, 308–319.
19. Mink, J.W.; Thach, W.T. Basal Ganglia Motor Control. III. Pallidal Ablation: Normal Reaction Time, Muscle Cocontraction, and Slow Movement. J. Neurophysiol. 1991, 65, 330–351.
20. Nambu, A.; Tokuno, H.; Takada, M. Functional Significance of the CorticoÁ/SubthalamoÁ/Pallidal ‘Hyperdirect’ Pathway. Neurosci. Res. 2002, 7.
21. Braak, H.; Del Tredici, K. Cortico-Basal Ganglia-Cortical Circuitry in Parkinson’s Disease Reconsidered. Exp. Neurol. 2008, 212, 226–229.

22. Cai, W.; Duberg, K.; Padmanabhan, A.; Rehert, R.; Bradley, T.; Carrion, V.; Menon, V. Hyperdirect Insula-Basal-Ganglia Pathway and Adult-like Maturity of Global Brain Responses Predict Inhibitory Control in Children. Nat. Commun. 2019, 10, 4798.
23. Wang, H.; Fan, L.; Song, M.; Liu, B.; Wu, D.; Jiang, R.; Li, J.; Li, A.; Banaschewski, T.; Bokde, A.L.W.; et al. Functional Connectivity Predicts Individual Development of Inhibitory Control during Adolescence. Cereb. Cortex 2020, bhaa383.
24. Greenhouse, I.; Oldenkamp, C.L.; Aron, A.R. Stopping a Response Has Global or Nonglobal Effects on the Motor System Depending on Preparation. J. Neurophysiol. 2012, 107, 384–392.
25. Levin, O.; Netz, Y.; Ziv, G. Behavioral and Neurophysiological Aspects of Inhibition—The Effects of Acute Cardiovascular Exercise. J. Clin. Med. 2021, 10, 282.
26. Aron, A.R. Cortical and Subcortical Contributions to Stop Signal Response Inhibition: Role of the Subthalamic Nucleus. J. Neurosci. 2006, 26, 2424–2433.
27. Aron, A.R.; Durston, S.; Eagle, D.M.; Logan, G.D.; Stinear, C.M.; Stuphorn, V. Converging Evidence for a Fronto-Basal-Ganglia Network for Inhibitory Control of Action and Cognition. J. Neurosci. 2007, 27, 11860–11864.
28. Badry, R.; Mima, T.; Aso, T.; Nakatsuka, M.; Abe, M.; Fathi, D.; Foly, N.; Nagiub, H.; Nagamine, T.; Fukuyama, H. Suppression of Human Cortico-Motoneuronal Excitability during the Stop-Signal Task. Clin. Neurophysiol. 2009, 120, 1717–1723.
29. Jahfari, S.; Waldorp, L.; van den Wildenberg, W.P.M.; Scholte, H.S.; Ridderinkhof, K.R.; Forstmann, B.U. Effective Connectivity Reveals Important Roles for Both the Hyperdirect (Fronto-Subthalamic) and the Indirect (Fronto-Striatal-Pallidal) Fronto-Basal Ganglia Pathways during Response Inhibition. J. Neurosci. 2011, 31, 6891–6899.
30. Mathis, J.; de Quervain, D.; Hess, C.W. Dependence of the Transcranially Induced Silent Period on the ‘instruction Set’ and the Individual Reaction Time. Electroencephalogr. Clin. Neurophysiol. Mot. Control 1998, 109, 426–435.
31. Fecteau, S.; Lassonde, M.; Théoret, H. Intrahemispheric Dysfunction in Primary Motor Cortex without Corpus Callosum: A Transcranial Magnetic Stimulation Study. BMC Neurol. 2006, 6, 21.
32. Kühn, A.A.; Brandt, S.A.; Kupsch, A.; Trottenberg, T.; Brocke, J.; Irlbacher, K.; Schneider, G.H.; Meyer, B.-U. Comparison of Motor Effects Following Subcortical Electrical Stimulation through Electrodes in the Globus Pallidus Internus and Cortical Transcranial Magnetic Stimulation. Exp. Brain Res. 2004, 155, 48–55.
33. Chu, H.-Y.; McIver, E.L.; Kovaleski, R.F.; Atherton, J.F.; Bevan, M.D. Loss of Hyperdirect Pathway Cortico-Subthalamic Inputs Following Degeneration of Midbrain Dopamine Neurons. Neuron 2017, 95, 1306–1318.e5.

34. Young, M.S.; Triggs, W.J.; Bowers, D.; Greer, M.; Friedman, W.A. Stereotactic Pallidotomy Lengthens the Transcranial Magnetic Cortical Stimulation Silent Period in Parkinson’s Disease. Neurology 1997, 49, 1278–1283.
35. Greenhouse, I.; Gould, S.; Houser, M.; Aron, A.R. Stimulation of Contacts in Ventral but Not Dorsal Subthalamic Nucleus Normalizes Response Switching in Parkinson’s Disease. Neuropsychologia 2013, 51, 1302–1309.
36. Nambu, A.; Takada, M.; Inase, M.; Tokuno, H. Dual Somatotopical Representations in the Primate Subthalamic Nucleus: Evidence for Ordered but Reversed Body-Map Transformations from the Primary Motor Cortex and the Supplementary Motor Area. J. Neurosci. 1996, 16, 2671–2683.
37. Deuschl, G.; Schade-Brittinger, C.; Krack, P.; Volkmann, J.; Schäfer, H.; Bötzel, K.; Daniels, C.; Deutschländer, A.; Dillmann, U.; Eisner, W. A Randomized Trial of Deep-Brain Stimulation for Parkinson’s Disease. N. Engl. J. Med. 2006, 355, 896–908.
38. Limousin, P.; Krack, P.; Pollak, P.; Benazzouz, A.; Ardouin, C.; Hoffmann, D.; Benabid, A.-L. Electrical Stimulation of the Subthalamic Nucleus in Advanced Parkinson’s Disease. N. Engl. J. Med. 1998, 339, 1105–1111.
39. Bäumer, T.; Hidding, U.; Hamel, W.; Buhmann, C.; Moll, C.K.E.; Gerloff, C.; Orth, M.; Siebner, H.R.; Münchau, A. Effects of DBS, Premotor RTMS, and Levodopa on Motor Function and Silent Period in Advanced Parkinson’s Disease. Mov. Disord. 2009, 24, 672–676.
40. Schroll, H.; Beste, C.; Hamker, F.H. Combined Lesions of Direct and Indirect Basal Ganglia Pathways but Not Changes in Dopamine Levels Explain Learning Deficits in Patients with Huntington’s Disease. Eur. J. Neurosci. 2015, 41, 1227–1244.
41. Beaumont, V.; Zhong, S.; Lin, H.; Xu, W.; Bradaia, A.; Steidl, E.; Gleyzes, M.; Wadel, K.; Buisson, B.; Padovan-Neto, F.E.; et al. Phosphodiesterase 10A Inhibition Improves Cortico-Basal Ganglia Function in Huntington’s Disease Models. Neuron 2016, 92, 1220–1237.
42. Vitek, J.L. Pathophysiology of Dystonia: A Neuronal Model. Mov. Disord. Off. J. Mov. Disord. Soc. 2002, 17, S49–S62.
43. Granert, O.; Peller, M.; Jabusch, H.-C.; Altenmüller, E.; Siebner, H.R. Sensorimotor Skills and Focal Dystonia Are Linked to Putaminal Grey-Matter Volume in Pianists. J. Neurol. Neurosurg. Psychiatry 2011, 82, 1225–1231.
44. Silberstein, P.; KuÈhn, A.A.; Kupsch, A.; Trottenberg, T.; Krauss, J.K.; WoÈhrle, J.C.; Mazzone, P.; Insola, A.; Di Lazzaro, V.; Oliviero, A. Patterning of Globus Pallidus Local Field Potentials Differs between Parkinson’s Disease and Dystonia. Brain 2003, 126, 2597–2608.
45. Zeuner, K.E.; Knutzen, A.; Granert, O.; Götz, J.; Wolff, S.; Jansen, O.; Dressler, D.; Hefter, H.; Hallett, M.; Deuschl, G. Increased Volume and Impaired Function: The Role of the Basal Ganglia in Writer’s Cramp. Brain Behav. 2015, 5, e00301.

46. Simonyan, K.; Cho, H.; Hamzehei Sichani, A.; Rubien-Thomas, E.; Hallett, M. The Direct Basal Ganglia Pathway Is Hyperfunctional in Focal Dystonia. Brain 2017, 140, 3179–3190.
47. Cotroneo, M.; Ciacciarelli, A.; Cosenza, D.; Casella, C.; Dell'Aera, C.; Grillo, F.; Fazio, M.C.; La Spina, P.; Musolino, R.F. Hemiballism: Unusual Clinical Manifestation in Three Patients with Frontoparietal Infarct. Clin. Neurol. Neurosurg. 2020, 188, 105612.