Neurophysiology of Gilles de la Tourette's Cerebellum: A Potential Target for Treatment?

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STATEMENT OF ORIGINALITY

My involvement in neuromodulation began earlier this year, when I commenced my Master degree in Clinical Neuroscience at University College London at the National Hospital for Neurology and Neurosurgery. During the first term, I completed a project on the role of the cerebellum in Gilles de la Tourette Syndrome (GTS) symptomology and the implications for potentially using brain stimulation techniques as therapy. The project served to expand my interest in neuromodulation techniques as a method of investigation as well as to reinforce my desire to become a physician who will conduct research with a clear clinical objective applicable to her patients. This project functioned as a precursor for my current research project in neuromodulation, which looks at differences in learning and plasticity functions between healthy controls and GTS patients, a thesis I am developing in a small team at the Sobell Department for Motor Neuroscience.

Following my current work in neuromodulation and neurophysiology, the intent of this original dissertation is to discuss a potential functional cerebellar role for GTS symptoms, including motor tics and associated cognitive deficits, so as to consider a potential intervention targeting underlying circuits. My future in clinical training and interest in patient management establishes a second objective for this work, which is to explore potential clinical treatments for this neuropsychiatric disorder using indirect or direct stimulation. Transcranial direct current stimulation (tDCS) can increase / decrease neuronal excitability and produce long lasting effects on plasticity. tDCS devices are easy to use and apply, as the machine itself consists of a stimulator connected to a sponge that is then directly applied over the target area.

Since a fair proportion of GTS patients are either resistant to many treatment options (such as pharmaceuticals) or experience side effects from medication and, as a result, are searching for an effective and safe alternative to their current therapy, tDCS can potentially offer an alternative option once strategic target structures are taken into consideration. The cerebellum is both a structure that can be easily accessed by tDCS as well as a strategic target, as more than fifty percent of CNS neurons reside here. Consequently, the cerebellum is rendered both an available and strategic structure for stimulation techniques such as direct and trans magnetic stimulation (TMS).

The role of the cerebellum in learning and plasticity process renders it a strategic and valuable structure to study when investigating potential treatment options for neuropsychiatric disorders such as GTS. The existing literature offers both evidence supporting the role of the cerebellum in GTS and the effectiveness of stimulation techniques as potential therapy for the disorder. As a neuroscientist and future clinician, it is of personal interest to invest my time in research with translational potential. I believe that investigating the physiological underpinnings of cerebral circuits with brain stimulation techniques will allow application of neuromodulation to target and modify aberrant excitability underlying symptoms of GTS. It is my objective to use my future clinical training to apply investigative findings to the development of potential treatments for neuropsychiatric disorders, specifically GTS.

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List of Abbreviations

ADHD	Attention deficit hyperactive disorder
BG	Basal ganglia
CbTC	Cerbellothalamocortical motor pathways
CS	Conditioned stimuli
DTI	Diffusion tensor imaging
GPi	Internal globus pallidis
GTS	Gilles de la Tourette syndrome
LTD	Long term depression
LTP	Long term potentiation
MRI	Magnetic resonance imaging
MS	Milliseconds
PAS	Paired associative stimulation
PET	Positron emission tomography
RT	Reaction time
SNpr	Substantia nigra pars reticulate
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
US	Unconditioned stimuli

INTRODUCTION

The interaction of the cerebellum with other cerebral regions, as well as its own discrete functions, presents it as a structure of growing interest in neuropsychiatry. Yet, the cerebellum's importance to neuropsychiatric disorders has often been debated (Gillig & Sanders, 2010; Konarski et al., 2005). Schizophrenia provides an example of a disease where investigations often disregard the role of the cerebellum. For many years, schizophrenia was thought to be a disorder primarily affecting the cerebrum (Andreasen & Pierson, 2008). Impairments in excitatory/inhibitory tone in the cerebellum for patients, however, now implies that the structure may be involved in cognitive impairments (Andreasen & Pierson, 2008). Studies looking at the cellular level of dysfunction have found abnormalities in regional distribution of cerebellar synaptic proteins in schizophrenic brains (Eastwood et al., 2001).

Since the neocerebellar region contains broadly distributed relays to the cerebral neocortex, and has been shown to have deviations in synaptic proteins, impairments in cognition potentially result from an inability to assimilate information and relay appropriate output signals to the cerebral cortex. Examples of such disorganization can be taken from auditory hallucinations (Andreasen, 1999; Andreasen et al., 1999; Andreasen et al.,1998). Yet, evidence for cerebellar abnormalities in schizophrenia is rather recent and is substantially less than evidence from other brain regions. Schizophrenia, however, also illustrates how the cerebellum has a more central and substantial role in the manifestation of symptomology of the disorder than previously contemplated, a role that could also be considered for other neuropsychiatric disorders, specifically Gilles de la Tourette Syndrome (GTS).

The manifestation of GTS symptoms can potentially be considered to involve motor aspects and properties of cognition. Studies show that the cerebellum is involved in motor (Hoppenbrouwers et al., 2008) and cognitive (Aasen et al., 2005; Eyler et al., 2004; Kiehl et al., 2005) impairments. Lesion studies have identified the role of the cerebellum in facilitation of cognition (Akshoomoff & Courchesne, 1992; Fiez et al., 1995; Keele & Ivry, 1990). Furthermore, lesions to the cerebellum indicate that it is involved in associative learning, as observed during eye blink conditioning (Attwell et al., 2002). The spontaneous and involuntary execution of movements, such as eye blinking in the case of motor tics, suggests motor learning dysfunctions. Additionally, the attention problems related to comorbid GTS and attention deficit hyperactivity disorder (ADHD) implies an involvement of cognitive faculties. The question is raised then as to potential neurophysiological motivations underlying GTS symptomology.

CEREBELLUM AS A LEARNING DEVICE

Motor tics are a principal symptom of GTS and can be sudden, brief and meaningless movements (simple motor tics). In some patients, tics may develop over time into sudden, more purposeful, longer duration movements (complex motor tics) (Leckman & Cohen, 1999). The underlying pathology of tics in GTS has not been fully elucidated, although the basal ganglia (BG) is known to be associated with these abnormal movements (Albin & Mink, 2006; Mink, 2001; Peterson, 2001), with dysfunctional GABA-ergic networks as one of the proposed pathologies (Kalanithi et al., 2005; Kataoka et al., 2010). Neuroimaging studies, however, have shown evidence for the role of the cerebellum in the pathogenesis of GTS (Bohlhalter et al., 2006; Lerner et al., 2007; Tobe et al., 2010; Pourfar et al., 2011).

Although the specific contribution of the cerebellum to this reciprocal network with the BG is not known, proposals as to the dysfunctional GABA-ergic networks underlying GTS pathology have been suggested (Lerner et al., 2012). As a mediator of inhibitory neurotransmission used principally by Purkinje cells (Nolte, 2002), GABA suppresses neuron firing by preventing excitatory influences of depolarization in the post-synaptic membrane (Alberts et al., 2012). As the main inhibitory system in the CNS, GABA-ergic neurons have a crucial role in modulation of chemical signalling (Alberts et al., 2012). Since Purkinje cells provide output from the cerebellum (Nolte, 2002), decrease in Purkinje cells could lead to decrease in cerebellar inhibitory output and modulation.

Abnormalities affecting cerebral morphology can alter the function of brain structures implicated in GTS, such as the cerebellum (Lerner et al., 2012). Magnetic resonance imaging (MRI) has shown changes in morphology of the cerebellum, with reduced volumes in crus I and lobules VI, VIIB and VIIIA for GTS patients, with greater volume reduction correlating to greater severity of tic symptoms. Reduction of volume implies that the structure has a prominent role in the generation of tics (Tobe et al., 2010), an implication that is supported by tracing studies.

These studies complete neurochemical characterization of specific neuronal pathways via axonal transport of tracers (Oztas, 2003) and have shown regional connectivity of Purkinje cells to primary motor cortices (Kelly & Strick, 2003). Decrease in volume, and potential accompanying loss of Purkinje cells, would disrupt corticocerebellar regulatory loops, increasing excitability of motor circuits, as shown specifically via the correlation to severity of tics (Tobe et al., 2010). Since the motor cortex is the final output stage before execution of movement, and is connected via the cortico-striatal-thalamo-network known to function abnormally in GTS, a greater severity of symptoms occurs. Motor tics result, possibly, due to an increase in excitation of cortical target areas (Tobe et al., 2010).

Abnormal excitability of the motor cortex via the cerebellum could be expected to cause motor tics possibly due to aberrations in certain structures of participating circuits. For example, the sub-thalamic nucleus, which receives input from the primary motor cortex, has disynaptic projections to the cerebellar cortex, and integrates BG cerebellar functions (Bostan & Strick, 2010). The di-synaptic projections from the sub-thalamic

nucleus to the cerebellum connect the structure to the cortico-striatal-thalamo network. Clusters of striatal neurons (matrisomes), once abnormally activated, lead to inhibition of the internal globus pallidis (GPi) or substantia nigra pars reticulata (SNpr) that would normally supress unwanted movement. Inhibition of the GPi or SNpr could cause disinhibition of the brainstem circuit, producing tics (Mink, 2001).

This process of aberrant circuit activity potentially also underlies mechanisms of plastic changes crucial for functions such as learning (Hallett & Chokroverty, 2005). Paired associative stimulation (PAS) is a method used to study synaptic plasticity of the motor cortex and involves repeated pairs of electrical stimulation to the median nerve in conjunction with transcranial magnetic stimulation (TMS). If the interval between both stimuli falls in the range of 21-25 milliseconds (ms), corticospinal activity is increased via long term potentiation (LTP) in the primary motor cortex. It has been observed that the modulation of cerebellar activity using transcranial direct current stimulation (tDCS) can abolish associative plasticity in the motor cortex induced by PAS, indicating that the PAS effect, and associative plasticity, is dependent on cerebellar activity (Hamada et al., 2012).

Pathologically affected activity of the cerebellum, such as that suggested to occur in GTS as a result of Purkinje cell loss induced by volume change, would present consequences to cerebellar modulation of plasticity. One possible effect could be hypoactivation of the cerebellum, leading to a lack of opposition to LTP and producing alternative patterns of motor learning. Specific dysfunctions in learning could include overlearning of abnormal associations, a product of aberrant cerebellar functioning (Leckman & Cohen, 1999), specifically in this proposal, a potential product of excessive LTP. When considering the involuntary and recurrent nature of tics (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®*, 2000) as a potential manifestation of overlearned patterns (memories), the question of the role of the dysfunctional cerebellum in these movements (tics) arises.

Specific learning pathways potentially involved in the reoccurrence of motor tics are also present in semi-reflexive motor learning involving the cerebellar cortex (Anderson & Steinmetz, 1994), deep cerebellar interpositus nucleus (Delgado-García & Gruart, 2002) and various brainstem nuclei (Raymond, Lisberger, & Mauk, 1996). Clinical observations report parents noting that their children's vocal tic symptoms often initiate with throat clearing or other cold related behaviour and persist after the cold subsides, as if normal behaviour repertoire related to the cold had been overlearned. Many motor tics, such as eye blinking and neck turning, are only abnormal and different from regular motor movements due to the intensity of reoccurrence and frequency (Leckman & Cohen, 1999). The previously proposed increase in excitability of motor circuits due to volume change in the cerebellum (Tobe et al., 2010), and the observed repetition of motor tics, suggests an overlearning of these motor actions in GTS patients. Overlearning of these motor movements implies similarities to learning processes of other rapid and involuntary behaviours, such as reflexive eyeblink conditioning (Leckman & Cohen, 1999), a basic learning mechanism mediated by the cerebellum (Logan & Grafton, 1995; Molchan et al., 1994; Thompson, 1990; Yeo, 1991).

Certain cells in the cerebellum have been shown to undergo learning induced changes during this conditioning. Purkinje cells in the cortex of the cerebellum appear to decrease their activity (Thompson, 1990) while those in the interpositus nucleus seem to do the inverse (Berthier & Moore, 1990). This functional activity is consistent with the anatomical inhibitory projections from the cerebellar cortex to the interpositus nucleus (Kim, 1997). Both the cerebellar cortex and interpositus nucleus receive information concerning the conditioned stimuli (CS) and unconditioned stimuli (US) of the eyeblink reflex and, therefore, both are capable of reinforcing associative learning (Kim, 1997) via processes of long term potentiation (LTP) (Racine et al., 1986) and long term depression (LTD) (Ito, 1989).

The observed changes in volume reported by neuroimaging studies (Hong et al., 2002; Tobe et al., 2010) and the associated reported increases in tic severity as a result of increased excitability of motor circuits (Tobe et al., 2010), can potentially be correlated to the aforementioned postulated lack of specific parts of the learning mechanism as a result of a possible loss of Purkinje cells (Tobe et al., 2010). LTD for example could result from strong synaptic stimulation in cerebellar Purkinje cells. If Purkinje cells are lost as a result of volume decrease, a subsequent decrease in LTD would lead to a deficient opposition to LTP (Churchland & Sejnowski, 1992). It must be mentioned, however, that it is not known whether volume changes cause abnormalities in synaptic activity or if volume changes reflect compensatory changes induced by intrinsic abnormalities in cellular excitability.

As previously mentioned, cerebellar LTD might serve as a 'forgetting mechanism' for information stored by increases in synaptic strength (Tsumoto, 1993), leading to a reoccurrence and presence of tics that can possibly be considered an overlearning of certain motor movements due to the lack of modulation of synaptic efficacy in learning. Loss of this form of plasticity would lead to an increase in synaptic strength (Purves et al., 2007) and a potential reinforcement or overlearning of motor movements (tics) in GTS patients.

CEREBELLUM IN COGNITION

Neuroimaging has demonstrated that the cerebellum has a central role in cognition, with activation occurring during a number of mental activities, such as directed attention (Allen et al., 1997) and might be considered to be central to certain cognitive deficits associated with symptoms observed in GTS (Lerner et al., 2012). GTS patients can be clinically associated with attention deficits (Georgiou et al., 1995) and GTS occurs frequently with ADHD (Comings & Comings, 1985; Spencer et al., 1995). Approximately 60% of GTS patients may present with ADHD (Channon et al., 1992; Comings, 1990).

Specific attention deficits including serial addition and block sequence span problems (Channon et al., 1992), render attention related symptoms one of the more pertinent comorbidity issues for GTS. Elucidation of the subtle neurocognitive deficits and the underlying mechanisms relating to attention have been attempted (Georgiou et al., 1995).

Functional magnetic resonance imaging (fMRI) has been used to examine the cerebellum during attention tasks in the absence and presence of motor response, with scans showing that attention activation can occur independently of motor involvement (Allen et al., 1997). The results highlight that motor activation requires attention and attention itself activates the cerebellum regardless of whether there is visual input or motor output present. The results underline functional independence of cerebellar activation by attention, as activation occurs even in the absence of movement. The dissociation is important, as it indicates that the cerebellum is a structure that directly influences neurobehavioral functions (Allen et al., 1997), specifically modulation of attention (Courchesne et al., 1994).

The role of the cerebellum in coordination of attention has been proposed as involving the neocerebellum (Courchesne et al., 1994), with deficits arising with lesions to the posterior lobule and lobules VI, VII (neocerebellum) (Schmahmann & Sherman, 1997). It has been observed that patients with autism exhibit impairments in attention (Kanner, 1968). Dysfunction at the level of the cerebellum in regards to attention would potentially prevent disengagement from one source to another, a task that requires quick and accurate alterations in patterns of neural response to sensory signals (Posner & Petersen, 1990; Posner et al., 1984).

Theories of cerebellar contribution to mental focus of attention have been tested by using cues at unpredictable time intervals to direct patients to voluntarily shift attention between auditory and visual stimuli. Patients with autism, another developmental disorder sharing symptoms that occur in GTS, show an inability to accurately shift attention rapidly, yet, when granted more time to complete the same task, are able to do so without difficulty. The results are similar to cerebellar lesion patients, whom also require several additional seconds to successively shift attention (Akshoomoff & Courchesne, 1992). In contrast, normal adults require much less time to accurately alternate between presentations (Sperling & Reeves, 1980; Weichselgartner & Sperling, 1987). Therefore, neural pathology in both these groups of patients appears to prevent optimal execution of shifts of attention, but not completely impede performance of attention shifts, an indication that the inability to optimally shift focus between stimuli is not a result of motor control problems, as the patients are able to perform the task accurately when given more time (Courchesne et al., 1994).

Additionally, volume reductions in vermal lobules VI-VII have been observed in autistic patients (Courchesne et al., 1994) as well as reduction in size of cerebellar hemispheres (Gaffney et al., 1987; Murakami et al., 1989). Furthermore, neuropathological findings in autistic patients show Purkinje neuron loss throughout the cerebellum, particularly in the same lobules showing volume reduction (Arin et al., 1991). The physioanatomical connections with other structures implicated in attention, such as the brainstem and thalamus, paired with substantial Purkinje cell loss, could be a contributing factor to attention dysfunctions in autism (Courchesne et al., 1994).

The study by Courchesne et al. serves as physioanatomical evidence of cerebellar involvement in attention by stating that the cerebellum has connections to the brainstem,

thalamic and parietal systems, all of which have been implicated in the ability to shift attention, as shown in studies of patients with focal lesions to the cerebellum (Akshoomoff & Courchesne, 1992). Specifically, the cerebello-thalamo-striato-cortical network appears to have a role in attention (Schneider et al., 2006). Different components of attention networks include subcortically located, alerting networks, which include the ascending reticular activating system, projecting to the brainstem and thalamus, up to the striatum and limbic system to form cortical projections. These mixed cortical-subcortical networks seem to be involved in disengaging attention focus (Schneider et al., 2006). Event related fMRI studies in ADHD patients have shown that patients recruit deviant brain regions for the mentioned networks, with more fronto-striatal-insular activation occurring during reorientation of attention (Konrad et al., 2006).

Although the cognitive, anatomical and functional proposals made thus far arise from studies and clinical observations in autistic and ADHD patients, MRI scans have shown changes in morphology of the cerebellum, with reduced volumes in crus I and lobules VI, VIIB and VIIIA for GTS patients, with greater volume reduction correlating to greater severity of tic symptoms (Tobe et al., 2010). Although autism shows reduction in volume for lobules of the vermis, whereas GTS shows reduction in volume for lobules of the hemispheres, these hemispheric lobules are often considered by a large number of cerebellar researchers as lateral extensions of corresponding vermal lobules (Anthoney, 1993). Keeping this anatomical consideration in mind, the affected lobules in autism and GTS can be considered, under this definition, to be comparable. Additionally, several studies in ADHD have also shown structural abnormalities in the cerebellum (Castellanos et al., 2001; Durston et al., 2004; Hill et al., 2003), with volume reductions in the right cerebellar hemispheres and vermis reported as correlating to attention problems (Castellanos et al., 2002). Since many GTS patients show comorbidity with ADHD, attention deficits in GTS can also be potentially attributed to these morphologic deviations.

Since autism, ADHD and GTS disturb similar structures, it can be proposed that there may be analogous underlying dysfunctions, mainly a loss of Purkinje cells, at the level of the cerebellum in respect to attention and might be considered to contribute to attention related impairments via the proposed brainstem, thalamic or cortical systems connecting to the structure (Posner & Petersen, 1990; Rafal et al., 1988; Rafal & Posner, 1987; Schneider et al., 2006).

A speculation could be that selective attention needed for enhancement of relative, pertinent signals and attenuation of irrelevant information might be most affected by disturbances in the cerebellum. A function such as this would be most noticed, perhaps, for situations requiring rapid, unpredictable and frequent shifts in attention. Cerebellar pathology might not eliminate attention operations completely, but simply dampen their ability to operate optimally, as patient performance approached normal reaction times (RTs) when given more time (Courchesne et al., 1994). Suboptimal operation of attention functions may be enough to accomplish certain tasks, which may account for such problems going unnoticed in certain patients.

IMPLICATIONS FOR TREATMENT

Further support for the importance of cerebellar inclusive networks in GTS is found in dystonia studies. Studies conducted in rodents show that projections between the cerebellum and BG cause dystonia (McCairn et al., 2013). Mouse models have shown that abnormal activity in the cerebellum alters BG function, leading to dystonic movements. Perfusion of Na^+ channel blockers in the cerebellum results in generalized dystonia. When di-synaptic links between the cerebellum and the BG were severed by lesioning the centro-lateral nucleus of the thalamus, cerebellar induced dystonia was alleviated, providing evidence for the involvement of the cerebellum in mediation of BG activity and generation of dystonia (Calderon et al., 2011).

Mouse models in DYT1 dystonia also support the role of the cerebellum in the disorder. DYT1 carriers exhibit abnormalities in the cerbellothalamocortical (CbTC) motor pathways. Diffusion tensor imaging (DTI) tractography analysis of both DYT1 knock-in mice and controls show that mutant mice exhibit significant CbTC tract changes in brainstem regions linking cerebellar and BG circuits analogous to those in humans. This provides further support for the role of cerebellar brain circuits in dystonia (Uluğ et al., 2011).

The central role of the cerebellum in dystonia raises the question as to possible therapies, such as non-pharmacological neuromodulation. The effects of DBS directly on the cerebellum were observed in dystonia patients, with various cases resulting in dramatic improvements (Cooper et al., 1980; Cooper et al., 1982). Pre and postoperative footage of a patient with dystonia in the left hand shows an improvement in gait and grasping. Another case shows a patient undergoing stimulation adjustment. The voltage increase causes the tonic contracture of the patient's hand to alleviate (Hornyak et al., 2001), showing the potential effectiveness of this target for dystonia.

Dystonic symptoms resemble GTS tics in their repetitive and involuntary movements. Dystonic tics in GTS, like movements in dystonia, are relatively slow and temporarily persistent actions such as twisting, pulling or squeezing movements. Studies looking at dystonic tics in GTS patients have found oculogyric deviation and dystonic neck movements to be the most common. When compared to patients exhibiting only clonic tics, it was found that dystonic tics are indeed typical motor manifestation of GTS and that this subgroup of patients does not differ from those with more common clonic tics (Jankovic & Stone, 1991).

This points to potential similarities in their contributing physiological cause, specifically the question of dysfunctions in overlearning of abnormal associations (Leckman & Cohen, 1999; Ruge et al., 2011). Potential physiological similarities could support the use of neuromodulation as a potential treatment for GTS. DBS use for movement disorders has led to its application as therapy for tic control in GTS (Vandewalle et al., 1999). The stimulation of the GPi has been shown to be effective for a subgroup of patients with severe GTS (Cannon et al., 2012; Houeto et al., 2005), which correlates to the structure's connection to the prefrontal cortex (Yoshida et al., 1996; Middleton et al., 2002), an area influencing cognition, which, in turn, relates to certain cognitive

symptoms in GTS (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®*, 2000).

However, surgeons have also reported that a variety of dyskinetic movements may improve following DBS of the dentate nucleus (Hitchcock 1973). Since DBS has been effective in patients with dystonia when applied to the cerebellum without prior knowledge of DBS mechanism, the treatment could possibly be extended to application in the cerebellum for GTS patients. DBS has been successfully applied to GTS patients (Ackermans et al., 2011; Okun et al., 2013; Porta et al., 2012; Savica et al., 2012; Visser-Vandewalle et al., 2003; Welter et al., 2008), with significant improvement in both tics and associated behavioural symptoms. Since these regions form part of cerebellar inclusive networks, including the cerbellothalamocortical pathway, therapy could possible include the cerebellum itself as a principal target area for stimulation, such as transcranial direct current stimulation (tDCS).

As a non-invasive brain stimulation technique, tDCS could be an effective and safe alternative to medication. Although there are many neuromodualtion techniques, tDCS is a relatively low cost, portable and well tolerated method (Coffman et al., 2014). tDCS has been useful in enabling treatments, for example of various neurological disorders (Schlaug et al., 2008). tDCS involves the application of small, non-painful electric currents and can be delivered via the use of sponge electrodes soaked in saline solution and delivered directly to the cerebellum, located 3 centimetres lateral to the inion (Galea et al., 2011), illustrating the easy localization of the cerebellum. Evidence shows that the cortex stimulated by the electrode can become more or less excitable for the period after stimulation ends (Liebetanz et al., 2002; Redfearn et al.,1964), with more lasting effects implicating LTP and LTD (Liebetanz et al., 2002; Nitsche et al., 2003). Since tDCS is a rather straightforward device to set up **(Figure 01)** and considering that the cerebellum is easily accessible transcranially as a stimulation target, it might be possible to have patients modulate cerebellar excitability themselves in the future.

CONCLUSION

Researching the relation of the cerebellum to different functions would expand theories as to the role of the structure in both motor and cognitive domains and provide a growing platform from which to evaluate the effectiveness of certain treatments for neuropsychiatric disorders. Management of GTS can include pharmaceuticals, yet, patients are often resistant to therapy (Robertson, 2000). Evidence provided in the form of mentioned literature establishes the cerebellum as a participant in functions related to GTS symptomology. The motivating role of the cerebellum in functions relating to motor and cognitive symptoms presents the possibility of proposing the cerebellum as a potential target for stimulation treatment in GTS.

Keeping a network view of these dysfunctions can aid in understanding the often comorbid nature of GTS, a complexity that can be attributed, potentially, to the multiple sources of disturbances (Leckman & Cohen, 1999). Utilizing non-pharmacological

neuromodulation techniques to elucidate organization plasticity, adaptation and integration of neural activity in circuits participating in abnormal motor and cognitive functions can potentially aid in predicting response to medication, establishing new interventions and guiding management of therapy options for neuropsychiatric patients.

FIGURE 01. TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

tDCS could be an effective and safe alternative to medication. tDCS is a relatively low cost, portable and well tolerated method (Coffman et al., 2014). The techniques involves the application of small, non-painful electric currents and can be delivered via the use of sponge electrodes soaked in saline solution and delivered directly to the cerebellum, located 3 centimetres lateral to the inion (Galea et al., 2011), illustrating the easy localization of the cerebellum.

Adapted from Medical Expo: The Medical Online Devices Exhibition (Online) ("TDCS electrical stimulator (2 channels) - DC-STIMULATOR - neuroConn," 2014). doi: http://www.medicalexpo.com/prod/neuroconn/tdcs-electrical-stimulators-2-channels-84837-546637.html

REFERENCES

Aasen, I., Kumari, V., & Sharma, T. (2005). Effects of rivastigmine on sustained attention in schizophrenia: an FMRI study. *Journal of Clinical Psychopharmacology*, *25*(4), 311–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16012272

Ackermans, L., Duits, A., van der Linden, C., Tijssen, M., Schruers, K., Temel, Y., … Visser-Vandewalle, V. (2011). Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain : A Journal of Neurology*, *134*(Pt 3), 832–44. doi:10.1093/brain/awq380

Akshoomoff, N. A., & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behavioral Neuroscience*, *106*(5), 731–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1445653

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2012). *Molecular Biology of the Cell, 5th Edition* (5th ed., p. 684). Garland Science. Retrieved from http://www.amazon.co.uk/Molecular-Biology-Cell-5th-Edition-ebook/dp/B0089NVFRM

Albin, R. L., & Mink, J. W. (2006). Recent advances in Tourette syndrome research. *Trends in Neurosciences*, *29*(3), 175–82. doi:10.1016/j.tins.2006.01.001

Allen, G., Buxton, R. B., Wong, E. C., & Courchesne, E. (1997). Attentional activation of the cerebellum independent of motor involvement. *Science (New York, N.Y.)*, *275*(5308), 1940–3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9072973

Anderson, B. J., & Steinmetz, J. E. (1994). Cerebellar and Brainstem Circuits Involved in Classical Eyeblink Conditioning : Reviews in the Neurosciences. Retrieved April 25, 2014, from http://www.degruyter.com/view/j/revneuro.1994.5.3/revneuro.1994.5.3.251/revneuro.1994.5.3.251.xml

Andreasen, N. C. (1999). A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Archives of General Psychiatry*, *56*(9), 781–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12884883

Andreasen, N. C., Nopoulos, P., O'Leary, D. S., Miller, D. D., Wassink, T., & Flaum, M. (1999). Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. *Biological Psychiatry*, *46*(7), 908–20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10509174

Andreasen, N. C., Paradiso, S., & O'Leary, D. S. (1998). "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophrenia Bulletin*, *24*(2), 203–18. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9613621

Andreasen, N. C., & Pierson, R. (2008). The role of the cerebellum in schizophrenia. *Biological Psychiatry*, *64*(2), 81–8. doi:10.1016/j.biopsych.2008.01.003

Anthoney, T. R. (1993). *Neuroanatomy and the Neurologic Exam: A Thesaurus of Synonyms, Similar-Sounding Non-Synonyms, and Terms of Variable Meaning* (p. 656). CRC Press. Retrieved from http://books.google.com/books?id=whrU2XEvGFIC&pgis=1

Arin, D. M., Bauman, M. L., & Kemper, T. L. (1991). The distribution of purkinje cell loss in the cerebellum in autism. *Neurology*, *41*(1), 307.

Attwell, P. J. E., Ivarsson, M., Millar, L., & Yeo, C. H. (2002). Cerebellar mechanisms in eyeblink conditioning. *Annals of the New York Academy of Sciences*, *978*, 79–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12582043

Berthier, N. E., & Moore, J. W. (1990). Activity of deep cerebellar nuclear cells during classical conditioning of nictitating membrane extension in rabbits. *Experimental Brain Research*, *83*(1). doi:10.1007/BF00232192

Bostan, A. C., & Strick, P. L. (2010). The cerebellum and basal ganglia are interconnected. *Neuropsychology Review*, *20*(3), 261–70. doi:10.1007/s11065-010-9143-9

Calderon, D. P., Fremont, R., Kraenzlin, F., & Khodakhah, K. (2011). The neural substrates of rapid-onset Dystonia-Parkinsonism. *Nature Neuroscience*, *14*(3), 357–65. doi:10.1038/nn.2753

Cannon, E., Silburn, P., Coyne, T., O'Maley, K., Crawford, J. D., & Sachdev, P. S. (2012). Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome. *The American Journal of Psychiatry*, *169*(8), 860–6. doi:10.1176/appi.ajp.2012.11101583

Castellanos, F. X., Giedd, J. N., Berquin, P. C., Walter, J. M., Sharp, W., Tran, T., … Rapoport, J. L. (2001). Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *58*(3), 289–95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11231836

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., … Rapoport, J. L. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA : The Journal of the American Medical Association*, *288*(14), 1740–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12365958

Channon, S., Flynn, D., & Robertson, M. (1992, October 24). Attentional deficits in Gilles de la Tourette syndrome. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*. Retrieved from http://eprints.ucl.ac.uk/126028/

Churchland, P. S., & Sejnowski, T. J. (1992). *The computational brain. Computational neuroscience.*

Coffman, B. A., Clark, V. P., & Parasuraman, R. (2014). Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage*, *85 Pt 3*, 895–908. doi:10.1016/j.neuroimage.2013.07.083

Comings, D. E. (1990). *Tourette syndrome and human behavior.*

Comings, D. E., & Comings, B. G. (1985). Tourette syndrome: clinical and psychological aspects of 250 cases. *American Journal of Human Genetics*, *37*(3), 435–50. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1684588&tool=pmcentrez&rendertype=abstract

Cooper, I. S., Upton, A. R. M., & Amin, I. (1980). Reversibility of Chronic Neurologic Deficits. Some Effects of Electrical Stimulation of the Thalamus and Internal Capsule in Man. *Stereotactic and Functional Neurosurgery*, *43*(3-5), 244–258. doi:10.1159/000102263

Cooper, I. S., Upton, A. R. M., & Amin, I. (1982). Chronic Cerebellar Stimulation (CCS) and Deep Brain Stimulation (DBS) in Involuntary Movement Disorders. *Stereotactic and Functional Neurosurgery*, *45*(3), 209–217. doi:10.1159/000101601

COURCHESNE, E., TOWNSEND, J., AKSHOOMOFF, N. A., SAITOH, O., YEUNG-COURCHESNE, R., LINCOLN, A. J., ... LAU, L. (1994). Impairment in shifting attention in autistic and cerebellar patients. *Behavioral Neuroscience*, *108*(5), 848–865. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=4259138

Delgado-García, J., & Gruart, A. (2002). The role of interpositus nucleus in eyelid conditioned responses. *The Cerebellum*, *1*(4), 289–308. doi:10.1080/147342202320883597

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®. (2000) (p. 943). American Psychiatric Pub. Retrieved from http://books.google.com/books?hl=en&lr=&id=w_HajjMnjxwC&pgis=1

Durston, S., Hulshoff Pol, H. E., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B., ... van Engeland, H. (2004). Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*(3), 332–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15076267

Eastwood, S. L., Cotter, D., & Harrison, P. J. (2001). Cerebellar synaptic protein expression in schizophrenia. *Neuroscience*, *105*(1), 219–29. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11483314

Eyler, L. T., Olsen, R. K., Jeste, D. V, & Brown, G. G. (2004). Abnormal brain response of chronic schizophrenia patients despite normal performance during a visual vigilance task. *Psychiatry Research*, *130*(3), 245–57. doi:10.1016/j.pscychresns.2004.01.003

Fiez, J. A., Raichle, M. E., Miezin, F. M., Petersen, S. E., Tallal, P., & Katz, W. F. (1995). PET Studies of Auditory and Phonological Processing: Effects of Stimulus Characteristics and Task Demands. *Journal of Cognitive Neuroscience*, *7*(3), 357–75. doi:10.1162/jocn.1995.7.3.357

Gaffney, G. R., Kuperman, S., Tsai, L. Y., Minchin, S., & Hassanein, K. M. (1987). Midsagittal magnetic resonance imaging of autism. *The British Journal of Psychiatry : The Journal of Mental Science*, *151*, 831–3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3502809

Galea, J. M., Vazquez, A., Pasricha, N., de Xivry, J.-J. O., & Celnik, P. (2011). Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. *Cerebral Cortex (New York, N.Y. : 1991)*, *21*(8), 1761–70. doi:10.1093/cercor/bhq246

Georgiou, N., Bradshaw, J. L., Phillips, J. G., Bradshaw, J. A., & Chiu, E. (1995). The Simon effect and attention deficits in Gilles de la Tourette's syndrome and Huntington's disease. *Brain*, *118*(5), 1305–1318. doi:10.1093/brain/118.5.1305

Gillig, P. M., & Sanders, R. D. (2010). Psychiatry, neurology, and the role of the cerebellum. *Psychiatry (Edgmont (Pa. : Township))*, *7*(9), 38–43. Retrieved from

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2952646&tool=pmcentrez&rendertype=abstract

Hallett, M., & Chokroverty, S. (2005). *Magnetic Stimulation In Clinical Neurophysiology* (p. 457). Butterworth-Heinemann Limited. Retrieved from http://books.google.co.uk/books/about/Magnetic_Stimulation_In_Clinical_Neuroph.html?id=f6trAAAAMAAJ&pgis=1

Hamada, M., Strigaro, G., Murase, N., Sadnicka, A., Galea, J. M., Edwards, M. J., & Rothwell, J. C. (2012). Cerebellar modulation of human associative plasticity. *The Journal of Physiology*, *590*(Pt 10), 2365–74. doi:10.1113/jphysiol.2012.230540

Hill, D. E., Yeo, R. A., Campbell, R. A., Hart, B., Vigil, J., & Brooks, W. (2003). Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology*, *17*(3), 496–506. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12959515

Hong, K.-E., Ock, S.-M., Kang, M.-H., Kim, C.-E., Bae, J.-N., Lim, M.-K., … Lee, J.-S. (2002). The segmented regional volumes of the cerebrum and cerebellum in boys with Tourette syndrome. *Journal of Korean Medical Science*, *17*(4), 530–6. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3054894&tool=pmcentrez&rendertype=abstract

Hoppenbrouwers, S. S., Schutter, D. J. L. G., Fitzgerald, P. B., Chen, R., & Daskalakis, Z. J. (2008). The role of the cerebellum in the pathophysiology and treatment of neuropsychiatric disorders: A review. *Brain Research Reviews*, *59*(1), 185–200. Retrieved from http://www.sciencedirect.com/science/article/pii/S0165017308000751

Hornyak, M., Rovit, R. L., Simon, A. S., & Couldwell, W. T. (2001). Irving S. Cooper and the early surgical management of movement disorders. Video history. *Neurosurgical Focus*, *11*(2), E6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16602679

Houeto, J. L., Karachi, C., Mallet, L., Pillon, B., Yelnik, J., Mesnage, V., … Agid, Y. (2005). Tourette's syndrome and deep brain stimulation. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(7), 992–5. doi:10.1136/jnnp.2004.043273

Ito, M. (1989). Long-term depression. *Annual Review of Neuroscience*, *12*, 85–102. doi:10.1146/annurev.ne.12.030189.000505

Jankovic, J., & Stone, L. (1991). Dystonic tics in patients with Tourette's syndrome. *Movement Disorders : Official Journal of the Movement Disorder Society*, *6*(3), 248–52. doi:10.1002/mds.870060309

Kalanithi, P. S. A., Zheng, W., Kataoka, Y., DiFiglia, M., Grantz, H., Saper, C. B., … Vaccarino, F. M. (2005). Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(37), 13307–12. doi:10.1073/pnas.0502624102

Kanner, L. (1968). Autistic disturbances of affective contact. *Acta Paedopsychiatrica*, *35*(4), 100–36. Retrieved from http://europepmc.org/abstract/MED/4880460

Kataoka, Y., Kalanithi, P. S. A., Grantz, H., Schwartz, M. L., Saper, C., Leckman, J. F., & Vaccarino, F. M. (2010). Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. *The Journal of Comparative Neurology*, *518*(3), 277–91. doi:10.1002/cne.22206

Keele, S. W., & Ivry, R. (1990). Does the cerebellum provide a common computation for diverse tasks? A timing hypothesis. *Annals of the New York Academy of Sciences*, *608*, 179–207; discussion 207–11. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2075953

Kelly, R. M., & Strick, P. L. (2003). Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a Nonhuman Primate. *J. Neurosci.*, *23*(23), 8432–8444. Retrieved from http://www.jneurosci.org/content/23/23/8432.abstract

Kiehl, K. A., Stevens, M. C., Celone, K., Kurtz, M., & Krystal, J. H. (2005). Abnormal hemodynamics in schizophrenia during an auditory oddball task. *Biological Psychiatry*, *57*(9), 1029–40. doi:10.1016/j.biopsych.2005.01.035

Kim, J. (1997). Cerebellar circuits and synaptic mechanisms involved in classical eyeblink conditioning. *Trends in Neurosciences*, *20*(4), 177–181. doi:10.1016/S0166-2236(96)10081-3

Konarski, J. Z., McIntyre, R. S., Grupp, L. A., & Kennedy, S. H. (2005). Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *Journal of Psychiatry & Neuroscience : JPN*, *30*(3), 178–86. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1089778&tool=pmcentrez&rendertype=abstract

Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., & Herpertz-Dahlmann, B. (2006). Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study. *Biological Psychiatry*, *59*(7), 643–51. doi:10.1016/j.biopsych.2005.08.013

Leckman, J. F., & Cohen, D. J. (Eds.). (1999). *Tourette's Syndrome – Tics, Obsessions, Compulsions: Developmental Psychopathology and Clinical Care* (p. 584). John Wiley & Sons. Retrieved from http://books.google.com/books?id=rZ-qKfBhQvIC&pgis=1

Lerner, A., Bagic, A., Simmons, J. M., Mari, Z., Bonne, O., Xu, B., … Hallett, M. (2012). Widespread abnormality of the γ-aminobutyric acid-ergic system in Tourette syndrome. *Brain : A Journal of Neurology*, *135*(Pt 6), 1926–36. doi:10.1093/brain/aws104

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain : A Journal of Neurology*, *125*(Pt 10), 2238–47. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12244081

Logan, C. G., & Grafton, S. T. (1995). Functional anatomy of human eyeblink conditioning determined with regional cerebral glucose metabolism and positron-emission tomography. *Proceedings of the National Academy of Sciences*, *92*(16), 7500–7504. doi:10.1073/pnas.92.16.7500

McCairn, K. W., Iriki, A., & Isoda, M. (2013). Global dysrhythmia of cerebro-basal ganglia-cerebellar networks underlies motor tics following striatal disinhibition. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *33*(2), 697–708. doi:10.1523/JNEUROSCI.4018-12.2013

Mink, J. W. (2001). Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatric Neurology*, *25*(3), 190–198. doi:10.1016/S0887-8994(01)00262-4

Molchan, S. E., Sunderland, T., McIntosh, A. R., Herscovitch, P., & Schreurs, B. G. (1994). A functional anatomical study of associative learning in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(17), 8122–6. Retrieved from

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=44557&tool=pmcentrez&rendertype=abstract

Murakami, J. W., Courchesne, E., Press, G. A., Yeung-Courchesne, R., & Hesselink, J. R. (1989). Reduced Cerebellar Hemisphere Size and Its Relationship to Vermal Hypoplasia in Autism. *Archives of Neurology*, *46*(6), 689–694. doi:10.1001/archneur.1989.00520420111032

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., ... Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology*, *553*(Pt 1), 293–301. doi:10.1113/jphysiol.2003.049916

Nolte, J. (2002). *The Human Brain: An Introduction to its Functional Anatomy STUDENT CONSULT, 5e (Human Brain: An Introduction to Its Functional Anatomy (Nolte)* (5th ed., p. 44). Mosby. Retrieved from http://www.amazon.com/The-Human-Brain-Introduction-Functional/dp/0323041310

Okun, M. S., Foote, K. D., Wu, S. S., Ward, H. E., Bowers, D., Rodriguez, R. L., ... Sanchez, J. C. (2013). A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. *JAMA Neurology*, *70*(1), 85–94. doi:10.1001/jamaneurol.2013.580

Oztas, E. (2003). Neuronal Tracing. *Neuroanatomy*, *2*, 2–5.

Peterson, B. S. (2001). Neuroimaging studies of Tourette syndrome: a decade of progress. *Advances in Neurology*, *85*, 179–96. Retrieved from http://europepmc.org/abstract/MED/11530427

Porta, M., Servello, D., Zanaboni, C., Anasetti, F., Menghetti, C., Sassi, M., & Robertson, M. M. (2012). Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. *Acta Neurochirurgica*, *154*(11), 2029–41. doi:10.1007/s00701-012-1497-8

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*, 25–42. doi:10.1146/annurev.ne.13.030190.000325

Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *4*(7), 1863–74. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6737043

Pourfar, M., Feigin, A., Tang, C. C., Carbon-Correll, M., Bussa, M., Budman, C., ... Eidelberg, D. (2011). Abnormal metabolic brain networks in Tourette syndrome. *Neurology*, *76*(11), 944–52. doi:10.1212/WNL.0b013e3182104106

Purves, D., Agustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., McNamara, J. O., & White, L. E. (2007). *Neuroscience [Hardcover]* (Fourth., p. 810). Sinauer Associates; 4th Edition edition. Retrieved from http://www.amazon.co.uk/Neuroscience-Dale-Purves/dp/0878936971

Racine, R. J., Wilson, D. A., Gingell, R., & Sunderland, D. (1986). Long-term potentiation in the interpositus and vestibular nuclei in the rat. *Experimental Brain Research*, *63*(1). doi:10.1007/BF00235658

Rafal, R. D., & Posner, M. I. (1987). Deficits in human visual spatial attention following thalamic lesions. *Proceedings of the National Academy of Sciences of the United States of America*, *84*(20), 7349–53. Retrieved from

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=299290&tool=pmcentrez&rendertype=abstract

Rafal, R. D., Posner, M. I., Friedman, J. H., Inhoff, A. W., & Bernstein, E. (1988). Orienting of visual attention in progressive supranuclear palsy. *Brain : A Journal of Neurology*, *111 (Pt 2*, 267–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3378136

Raymond, J. L., Lisberger, S. G., & Mauk, M. D. (1996). The Cerebellum: A Neuronal Learning Machine? *Science*, *272*(5265), 1126–1131. doi:10.1126/science.272.5265.1126

REDFEARN, J. W. T., LIPPOLD, O. C. J., & COSTAIN, R. (1964). Preliminary Account of the Clinical Effects of Polarizing the Brain in Certain Psychiatric Disorders. *The British Journal of Psychiatry*, *110*(469), 773–785. doi:10.1192/bjp.110.469.773

Robertson, M. M. (2000). Tourette syndrome, associated conditions and the complexities of treatment. *Brain*, *123*(3), 425–462. doi:10.1093/brain/123.3.425

Ruge, D., Tisch, S., Hariz, M. I., Zrinzo, L., Bhatia, K. P., Quinn, N. P., … Rothwell, J. C. (2011). Deep brain stimulation effects in dystonia: time course of electrophysiological changes in early treatment. *Movement Disorders : Official Journal of the Movement Disorder Society*, *26*(10), 1913–21. doi:10.1002/mds.23731

Sanders, R. D., & Gillig, P. M. (2010). Gait and its assessment in psychiatry. *Psychiatry (Edgmont (Pa. : Township)]*, *7*(7), 38–43. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2922365&tool=pmcentrez&rendertype=abstract

Savica, R., Stead, M., Mack, K. J., Lee, K. H., & Klassen, B. T. (2012). Deep brain stimulation in tourette syndrome: a description of 3 patients with excellent outcome. *Mayo Clinic Proceedings*, *87*(1), 59–62. doi:10.1016/j.mayocp.2011.08.005

Schlaug, G., Renga, V., & Nair, D. (2008). Transcranial direct current stimulation in stroke recovery. *Archives of Neurology*, *65*(12), 1571–6. doi:10.1001/archneur.65.12.1571

Schmahmann, J. D., & Sherman, J. C. (1997). Cerebellar cognitive affective syndrome. *International Review of Neurobiology*, *41*, 433–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9378601

Schneider, M., Retz, W., Coogan, A., Thome, J., & Rösler, M. (2006). Anatomical and functional brain imaging in adult attention-deficit/hyperactivity disorder (ADHD)–a neurological view. *European Archives of Psychiatry and Clinical Neuroscience*, *256 Suppl* , i32–41. doi:10.1007/s00406-006-1005-3

Spencer, T., Biederman, J., Harding, M., Wilens, T., & Faraone, S. (1995). The relationship between tic disorders and Tourette's syndrome revisited. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*(9), 1133–9. doi:10.1097/00004583-199509000-00009

Sperling, G., & Reeves, A. (1980). *Attention and Performance VIII* (p. 822). Psychology Press. Retrieved from http://books.google.com/books?hl=en&lr=&id=K5pa9DlnzFYC&pgis=1

TDCS electrical stimulator (2 channels) - DC-STIMULATOR - neuroConn. (2014). Retrieved April 30, 2014, from http://www.medicalexpo.com/prod/neuroconn/tdcs-electrical-stimulators-2-channels-84837-546637.html

Thompson, R. F. (1990). Neural mechanisms of classical conditioning in mammals. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *329*(1253), 161–70. doi:10.1098/rstb.1990.0161

Tobe, R. H., Bansal, R., Xu, D., Hao, X., Liu, J., Sanchez, J., & Peterson, B. S. (2010). Cerebellar morphology in Tourette syndrome and obsessive-compulsive disorder. *Annals of Neurology*, *67*(4), 479–87. doi:10.1002/ana.21918

Tsumoto, T. (1993). Long-term depression in cerebral cortex: a possible substrate of "forgetting" that should not be forgotten. *Neuroscience Research*, *16*(4), 263–270. doi:10.1016/0168-0102(93)90036-P

Uluğ, A. M., Vo, A., Argyelan, M., Tanabe, L., Schiffer, W. K., Dewey, S., … Eidelberg, D. (2011). Cerebellothalamocortical pathway abnormalities in torsinA DYT1 knock-in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(16), 6638–43. doi:10.1073/pnas.1016445108

Vandewalle, V., van der Linden, C., Groenewegen, H., & Caemaert, J. (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *The Lancet*, *353*(9154), 724. doi:10.1016/S0140-6736(98)05964-9

Visser-Vandewalle, V., Temel, Y., Boon, P., Vreeling, F., Colle, H., Hoogland, G., … van der Linden, C. (2003). Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. Report of three cases. *Journal of Neurosurgery*, *99*(6), 1094–100. doi:10.3171/jns.2003.99.6.1094

Weichselgartner, E., & Sperling, G. (1987). Dynamics of automatic and controlled visual attention.

Welter, M.-L., Mallet, L., Houeto, J.-L., Karachi, C., Czernecki, V., Cornu, P., … Agid, Y. (2008). Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Archives of Neurology*, *65*(7), 952–7. doi:10.1001/archneur.65.7.952

YEO, C. H. (1991). Cerebellum and Classical Conditioning of Motor Responses. *Annals of the New York Academy of Sciences*, *627*(1 Activity-Driv), 292–304. doi:10.1111/j.1749-6632.1991.tb25933.x

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