Deep Brain Stimulation: A Potential Therapy for Epilepsy and Movement Disturbances in Autism Spectrum Disorders?

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Abstract

Within the last ten years, deep brain stimulation has transformed the treatment of a variety of neurological disorders. The principle of deep brain stimulation relies on the continuous electrical stimulation of neural brain structures through implanted electrodes. The therapeutic effects of this technology are most evident in the field of movement disorders where this treatment has become routine for advanced Parkinson’s disease patients. More recently, preliminary studies on the use of this technique in epileptic patients suggest that this therapy may be effective in decreasing seizure activity in these subjects. The use of deep brain stimulation is particularly valuable because of its success in treating the proportion of patients whose conditions are otherwise medically refractive.

The present success achieved with the application of deep brain stimulation in the treatment of movement disorders warrants the consideration of its future application to related disorders. These disorders include the group of heterogeneous autism spectrum disorders. Individuals diagnosed with autism spectrum disorders present with unique movement disturbances that are similar to the disturbances that have been defined in most movement disorders. In addition, approximately one third of autistic individuals develop epilepsy and a considerable minority of autistic individuals who do not present with seizures, show epileptiform discharges. This abnormal brain activity has been suggested to be involved in the cognitive, language and behavioral deficits characteristic of these disorders.

Despite its success in treating various movement disorders in the clinical setting, the exact mechanism of how deep brain stimulation works is still unclear. Complete understanding of the mechanisms of deep brain stimulation
will allow for the optimization of present and future applications of this technology. The first goal of this essay is to discuss the recent findings on the therapeutic effects of deep brain stimulation within the central nervous system, particularly in the treatment of Parkinson’s disease. The second is, specifically, through assessment of the benefits of using this technology in epileptic patients, to propose future experimental studies aimed at investigating the potential therapeutic properties of deep brain stimulation technology in treating autism spectrum disorders.

The autism spectrum is the general term used to describe life-long developmental disorders of brain function with differing severity (Tuchman & Rapin, 2002). Autism spectrum disorders (ASDs) may occur in as many as 1/100 to 1/200 live births with diagnosis usually occurring before the age of 3 (Chez, Memon, & Hung, 2004). Approximately 30% of individuals with ASD present with epilepsy/epileptic electroencephalography (EEG) profiles. This epileptic activity might contribute to the regression in language and social skills that occurs in about 40% of individuals with ASD between the ages of 2 and 10 years (Ballaban-Gil & Tuchman, 2000; Di Martino & Tuchman, 2001; Sharifi & Wiznitzer, 2004b; Spence, & Trevathan, 2004). A significant number of individuals with ASD also present with distinct movement disorders that might involve specific motor system dysfunction affecting the basal ganglia among other neural structures (Vilensky, Damasio, & Maurer, 1981). The current classifications of ASDs however, fail to incorporate descriptions of motor disturbance symptoms in children with ASD (Ballaban-Gil & Tuchman, 2000; Brasic, 1999; Leary & Hill, 1996; Marsden, 1984). Additionally these ASD classifications do not consider the occurrence of epilepsy and epileptic activity in affected individuals.

At present there is no cure for the disorders on the autism spectrum and treatment usually involves comprehensive behavioral therapy, the goal of which is to equip individuals with skills that will facilitate their daily activities (Nayate, Bradshaw, & Rinehart, 2005). The application of deep brain stimulation (DBS) to treat individuals on the autism spectrum may be a novel and innovative method of treatment. This technology may be particularly useful for the subset of individuals with ASD that present with intractable epilepsy and characteristic movement disorders, and may represent a distinct subgroup of ASD patients.
What Is Deep Brain Stimulation?

DBS as it is used today involves the electrical stimulation of neuronal elements by electrodes placed in the brain using a stereotactic method (Benabid, 2003; Lozano, Dostrovsky, Chen, & Ashby, 2002). This method is commonly used in neurosurgery and involves using a three dimensional coordinate system along with radiological methods to precisely locate target points in the brain for electrode placement. Electrodes typically have an approximate contact area of 6mm\(^2\) and deliver a current of approximately 3mA (Lozano et al., 2002). Electrodes are connected to a small battery operated pulse generator which delivers currents at a predetermined frequency, intensity and duration which are programmed by a neurologist. The generator is placed under the patient’s skin, usually over the chest wall (Lozano et al., 2002).

The concept of using electrical brain stimulation to treat clinical disorders dates back to as early as 76 AD, where the Greek physician, Dioscorides was said to have treated seizures with the electric torpedo ray (Kellaway, 1946). During the middle and second half of the 18th centuries Leyden jars, an early form of a capacitor, were used for similar purposes (Boling, Olivier, & Fabinyi, 2002). Despite the early introduction and use of electrical brain stimulation, it is only within the last decade that this technology has begun to reach its vast clinical potential. This is thought to be due to the significant advances made in the basic and clinical neurosciences (Breit, Schulz, & Benabid, 2004).

More recently, the therapeutic role of DBS has been most extensively studied in movement disorders (Lozano & Hamani, 2004; McIntyre, Savasta, Walter, & Vittek, 2004). Benabd et al. pioneered this move in 1987 when they showed that high frequency stimulation of the thalamus (100Hz and higher) produced results similar to that of thalamotomy (lesioning of the thalamus) – that is, suppression of tremors in Parkinson’s disease (PD) patients resistant to drug therapy (Benabd, Pollak, Louveau, Henry, & de Rougemont, 1987). These findings appear to be inconsistent with fundamental electrophysiological principles, from which one might predict activation and excitation of neural elements in response to simulation. Indeed, one of the first uses of deep brain stimulation back in 1954 was to activate a pain inhibitory pathway to alleviate medically intractable pain in subjects (Gybel & Sweet, 1989).

The discovery that the application of DBS to certain neural structures could produce the same results as the lesioning of those structures in a controllable, reversible and therefore safer manner initiated a surge in basic and clinical research on DBS technology. In comparison to lesioning methods, DBS
proved to be dependable and safe (Ashkan, Wallace, Bell, & Benabid, 2004; Lozano & Hamani, 2004).

Within the years that followed its first use, the target structures for DBS in PD patients extended from the thalamus to include the palladium and finally the subthalamic nucleus (STN) (Ashkan et al., 2004). Other movement disorders that have been successfully treated with this technology since then are dystonia (Marks, 2005; Starr et al., 2004) and tremors (Breit et al., 2004). The majority of DBS treated patients report complete cessation of or significant reductions in associated symptoms (Benabid, 2003; Breit, Schulz, & Benabid, 2004; Lozano, & Hamani, 2004; McIntyre, Savasta, Walter, & Vitek, 2004). More recently, DBS technology has been clinically studied in the treatment of conditions outside of the movement disorders field (Benabid, 2003). These areas include: psychosurgery (nucleus accumbens and subthalamic nucleus) (Mayberg et al., 2005); cluster headaches (posterior hypothalamus) (Leone, 2004; Leone et al., 2004; Schoenen et al., 2005); Tourette syndrome (Temel & Visser-Vandewalle, 2004), obesity (anterior hypothalamus, ventromedial and lateral) (Benabid, 2003) and epilepsy (anterior nuclei of the thalamus and subthalamus).

The preliminary achievements of DBS technology in treating epileptic symptoms, coupled with its established success in PD warrants the consideration of its future application to treat individuals with ASDs. This technology may be particularly beneficial to the subpopulation of individuals with ASD that display both epileptic and movement disorder characteristics (See Figure 1).

Figure 1. Proposed schematic for the relation between autism spectrum disorders, movement disorders and epileptiform activity. The possible relationship between these three disorders warrants investigative studies into the potential therapeutic use of deep brain stimulation in autism.

The group of individuals that fall in the overlap between ASD, motor disorders and epilepsy may represent a subset of individuals that could stand to benefit from DBS.
These individuals may represent the most severely affected ASD patients, who might stand to gain the most benefit from the new and innovative therapies. More importantly, this overlap may symbolize an underlying dysfunction in neurological structures common to all three disorders providing a rationale for the consideration of similar modes of treatment for these patients and a new approach to clinical and experimental studies.

The Therapeutic Application of High Frequency Deep Brain Stimulation in Parkinson's Disease and Epilepsy

Basal Ganglia Dysfunction in Parkinson Disease and Epilepsy

The term "basal ganglia" is the collective name given to a group of nuclei located on both sides of the brain. These nuclei are: the caudate nucleus and putamen (both of which make up the striatum), the globus pallidus (internal (GPI) and external segments), the subthalamic nucleus (STN) and substantia nigra (consisting of the pars compacta (SNc) and pars reticula (SNr)). The nuclei of the basal ganglia are intricately involved in the planning and execution of movement (Ganong, 2001).

The striatum is the main input nuclei of the basal ganglia, receiving excitatory glutaminergic afferents mainly from the cerebral cortex. The output nuclei, GPI and SNr are both inhibitory γ-amino butyric acid (GABA)ergic that project to the motor and premotor cerebral cortices by way of the thalamus (Weiner & Lang, 1989). Abnormalities in the electrical signaling pathways involved in the initiation, execution and termination of movement usually involve malfunction of the basal ganglia structures and can result in movement/motor disorders.

The term movement disorder is typically used to describe symptoms that include a loss of normal voluntary movement (akinesia) or excessive abnormal involuntary movements (dyskinesia) (Weiner & Lang, 1989). Conventionally, most neurologists exclude disorders that are due solely to cerebellar, spinal cord, motor neuron, peripheral nerve or muscle dysfunction. As a result, a vast majority of movement disorders are associated with basal ganglia dysfunction (Weiner & Lang, 1989). However, motor disorders typically involve more widespread lesions in different areas of the brain (Marsden, 1984).

Parkinson’s Disease

In one of the most common motor disorders of basal ganglia function, Parkinson’s disease (PD), there is severe disruption of basal ganglia function
due to destruction of nuclei within the substantia nigra and surrounding areas (Betchen & Kaplitt, 2003; Lozano et al., 2002; Marsden, 1984). The net result is a progressive loss of inhibitory dopaminergic cells within the basal ganglia and pronounced abnormalities in the spontaneous activity and sensorimotor responses of basal ganglia nuclei (Lang & Lozano, 1998). Most PD patients experience tremors, bradykinesia or slowness in movement, muscle stiffness, postural reflex impairment and balancing and walking difficulties (Weiner & Lang, 1989). In the later stages of PD, some patients also develop signs of dementia, thought to be associated with cortical acetylcholine loss (Marsden, 1984).

Perhaps the earliest treatment for PD involved lesioning of certain target areas in the brain such as the thalamus and globus pallidus (Lang et al., 1998). The post-operative difficulties and morbidity coupled with the emergence of potentially beneficial levodopa therapy in the 1970’s led to an almost complete abandonment of the surgical treatment for this disorder. The pharmacological treatment of PD was initially successful in compensating for the loss of dopamine production in PD. However, after a few years of dopaminergic therapy, levodopa-induced dyskinesias and motor fluctuations lead to a progressive worsening of symptoms in patients. Patients eventually develop resistance to dopaminergic therapy and some experience drug related side effects such as psychosis (Rascol, Payous, Ory, Ferreira, Brefel-Courbon, & Montastruc, 2003).

The failure of dopaminergic therapy and surgical approaches to treat all PD patients opened the door for novel approaches to complement the existing therapies, namely DBS, particularly high frequency DBS (HF-DBS) (Benabid et al., 2005; Lozano & Hamani, 2004). Currently, the pre-requisite for HF-DBS in PD is disabling dyskinesias after maximal medical therapy or patients in the advanced state of the disease who are either ineligible for or non-responsive toward conventional therapies (Benabid et al., 2005; Lozano & Mahant, 2004). The common target structures for HF-DBS in PD patients are the GPi and STN both of which mimic levodopa therapy without many of its adverse side effects (Lozano & Mahant, 2004). HFS of the STN improves motor function by at least 60% and greatly improves PD patient quality of life (Benabid et al., 2005; Lozano & Mahant, 2004).

HF-DBS has gained acceptance and become the neurosurgical treatment of choice for PD patient’s refractory to levodopa treatment and/or its debilitating side effects (Benabid et al., 2005; Lozano & Mahant, 2004). More than 30,000 patients with PD have already been treated with HF-DBS and this number is rising progressively (Lozano & Hamini, 2004). A reported
80% of the patients with PD that have undergone deep brain stimulation in clinical trials have had total or significant reduction in their tremor and related disabilities (Cigna Health Care, 2005). Further understanding of the mechanism(s) of action of HF-DBS is thought to be crucial for improved outcome particularly in the treatment of refractory features of PD (Lozano & Hamini, 2004; Lozano & Mahant, 2004).

**Epilepsy**

Epilepsy is not classified as a motor disorder, however, there is increasing evidence suggesting a role for the basal ganglia in epileptic seizures (Deransart & Depaulis, 2002; Verchueil & Hirsch, 2002). Epilepsy is defined as a chronic disorder of brain function typified by recurrent seizures of any kind (Porter, 1993). This definition excludes febrile seizures as well as seizures that occur during acute trauma, infection, or metabolic illness. Epilepsy is characterized and diagnosed in most cases by distinct electroencephalography (EEG) profiles, notably spike-wave activity during seizures (Binnie, 1993). It is well known that epileptiform EEG discharges can occur in the absence of obvious seizures in both epileptic and non-epileptic individuals (Naquet, 1983). The name given to this kind of EEG activity is "subclinical" or "interictal" discharges (Binnie, 2003). In patients with ongoing epilepsy, interictal discharges occur in up to 80% of the cases (Ajmone & Zivin, 1970).

The risk of developing epilepsy in the normal population is about 1%; however, the risk is almost ten times as high in certain populations such as in patients with ASDs (Canitano, 2007). Epilepsies are one of the most common neurological disorders affecting at least twice as many persons in North America as PD (Theodore et al., 2006). Unlike PD, however, the neural networks involved in the pathophysiology of epilepsy are less well defined. This is partly due to the distinct heterogeneity of this disorder (Litt, 2003). Similar to the treatment of PD, the surgical treatment of epilepsy dates back to the early 20th century. Epileptogenic areas of the brain were removed or resected to treat epileptic patients (Polkey & Binnie, 1993). However, as the technique gained popularity it was clear that resective surgery was not suitable for all patients with chronic epilepsy. Despite the unparalleled progress in the pharmacotherapy of epilepsy within the last two decades, the current use of this therapy is still shrouded by several limiting factors (Deckers, Genton, Sills, & Schmidt, 2003; Mohanraj & Brodie, 2003). Not all epileptic patients improve, actually, as many as 25-30% of these patients still experience seizures despite being on optimal therapy. Similar to drug therapy in PD, the drug treatment in epilepsy is often accompanied by many side effects (Rascol et al., 2003).
Another treatment option that has developed within the last century is vagus nerve stimulation (VNS). VNS has proven to be very effective in reducing seizure frequency and is now an accepted and registered epileptic therapy, received by more than 15,000 patients worldwide (Ben Menachem, 2002). VNS is similar to deep brain stimulation in that it involves the implantation of electrodes and their connection to a pulse generator. However, in VNS, the electrode is placed in the left vagus nerve (Ben Menachem, 2002; Guberman, 2004; Litt, 2003). The affected neuronal networks are thought to include the thalamus and other limbic structures. Norepinephrine is thought to mediate the antiseizure activity of VNS (Ben Menachem, 2002; Guberman, 2004; Litt, 2003).

VNS does not replace drug therapy, but improves outcome in the population of intractable epilepsy patients that are unable to have resective surgery or those that have had surgery with poor results. Additionally, VNS is also beneficial for patients who have developed resistance to drug treatment (Ben Menachem, 2002; Guberman, 2004). In the studies where children were included, a 50% reduction in the number of seizures after 18 months from starting was reported (Ben Menachem, 2002).

Trials involving the electrical stimulation of the brain in epileptic patients proceeded alongside studies of VNS in the 1970s, initiated primarily by Dr. Irvin Cooper (Rosenow, Das, Rovit, & Couldwell, 2002). Within the last decade, there has been resurgence in the application of electrical brain stimulation as a therapy in epilepsy (Hamani, Hodaie, & Lozano, 2005a; Loddenkemper et al., 2001; Litt, 2003). These renewed efforts have been facilitated by an advancement in the understanding of the mechanisms of epileptic seizures derived mainly from experimental models of epilepsy in laboratory animals (Benabid, Minotti, Koudsie, de Saint, & Hirsch, 2002; Goodman, 2004; Hamani et al., 2005a). These studies implicate the thalamus and some of the structures in the basal ganglia such as the STN, globus pallidus and striatum in the control of seizure and epileptiform activity leading to the concept of the ‘nigral control of epilepsy system’ (NCES) (Benabid et al., 2005; Deransart, Vercueil, Marescaux, & Depaulis, 1998; Loddenkemper et al., 2001; Vercueil & Hirsh, 2002).

Benabid and colleagues have targeted the STN for DBS in patients with intractable epilepsy. They report significant reductions in seizure frequencies in these subjects (Benabid et al., 2002). Other groups have reported decreased seizure activity in patients after stimulation of the caudate (Sramka & Chkhenkeli, 1990), cerebellum (Chkhenkeli & Chkhenkeli, 1997; Sramka & Chkhenkeli, 1990), anterior thalamus (Hodaie, Wennberg, Dostrovsky, &
Lozano, 2002), central median thalamic nucleus (Velasco, Velasco, Jimenez, Velasco, & Marquez, 2001) and hippocampus (Velasco et al., 2000).

Based on the studies to date, it is evident that outcome is dependent on the kind of epilepsy being treated as well as the neural structures stimulated and the parameters of stimulation such as frequency, current intensity and duration. The application of DBS to treat epilepsy is in its infancy and larger scaled clinically controlled trials are being conducted to fully assess the effect of DBS in epilepsy.

**Epilepsy/Epileptic Activity and Movement Disturbances in Autistic Spectrum Disorders**

**Rationale for the Application of High Frequency Deep Brain Stimulation Epilepsy/Epileptic Activity in ASD**

Approximately 30-39% of individuals with ASD undergo a regression in language and social skills between 2 and 10 years of age (Spence, Sharifi, & Wiznitzer, 2004; Trevathan, 2004). Epidemiological evidence from several studies suggest that this regression is linked to the onset of epileptiform activity (Ballaban-Gil & Tuchman, 2000; Chez, Memon, & Hung, 2004; Trevathan, 2004; Tuchman & Rapin, 2002).

Epilepsy is more common among children with ASD than among other children in the general population (Trevathan, 2004). The frequency of epileptiform activity is also reportedly higher in autistic individuals than in clinically epileptic patients (Chez et al., 2004; Tuchman & Rapin, 2002). As many as 50% of autistic children with verbal agnosia (lost ability to comprehend the spoken word) may display abnormal epileptiform activity on prolonged EEG recordings. This percentage is even higher in children below 18 months (Chez et al., 2004).

The actual reported frequency of epilepsy in autistic children varies between 5% and 39% (Trevathan, 2004; Tuchman & Rapin, 2002). This variation is thought to be due to factors such as differences in the age and severity of cognitive dysfunction in participants, inclusion and exclusion criteria as well as the date during which the study was conducted. Other factors include the delayed diagnosis of epilepsy, seizures or epileptic activity. Complex partial-onset seizures are easily confused with lack of social responsiveness and the repetitive movements that characterize autism (Ballaban-Gil & Tuchman, 2000; Willemsen-Swinkels & Buitelaar, 2002). In addition, the diagnoses of epileptiform abnormalities in the absence of seizures is often missed since the identification of these patterns requires video-EEG monitoring for
prolonged periods of time or during sleep (Ballaban-Gil & Tuchman, 2000; Di Martino & Tuchman, 2001; Trevathan, 2004). These factors all challenge the establishment of a relationship between epileptic activity and social and cognitive regression in individuals with ASD.

Despite this challenge however, experimental evidence strongly points to a causal role for epileptiform discharges in behavioral problems, regression and transitory cognitive impairment (TCI) (Binnie, 2003; Pressler, Robinson, Wilson, & Binnie, 2005). Active suppression of interictal discharges by pharmacological treatment has been demonstrated to improve behavior in children with behavioural problems and epilepsy (Pressler et al., 2005).

A link between epileptiform discharge and cognitive function may be further supported by a subgroup of epileptic patients that present with the hallmark feature of continuous spike waves during sleep. This group is recognized as having a distinct syndrome of idiopathic partial seizures. Many of these children show regression in cognitive function and individuals with specific loss of acquired language skills are described as having Landau-Kleffner syndrome (LKS). LKS is a rare syndrome in which a loss in language is correlated with either epileptiform EEG activity or clinical seizures (McVicar & Shinnar, 2004). Children with LKS develop subacute verbal auditory agnosia within the first five years of life. Further regression in some of these children includes impaired speech production, mutism and the inability to respond to non-verbal sounds.

The role of epileptiform activity in the pathogenesis of ASDs is still controversial. On one extreme is the belief that epileptiform activity is not linked to the pathogenesis of autism. Conversely, some believe that there may be a causal role of epileptiform activity in regression (McVicar & Shinnar, 2004; Trevathan, 2004). In the middle are some investigators and clinicians who support the belief that in both the cases of LKS and ASD, epilepsy and epileptiform abnormalities may be a separate manifestation indicative of dysfunction in common brain areas (Di Martino & Tuchman, 2001). However, the overall neuropsychological function in patients with disorders on the autism spectrum that present with epileptiform activity is determined by several factors. These factors include but are not limited to the pathophysiology of the disorder, medication, genetic factors,

**Movement disturbances in Autistic Spectrum Disorder**

There is debate over whether distinct movement disorders accompany the social and behavioral disorders of ASD. Furthermore, the role they may play
Preliminary studies on movement disturbances were conducted in the early eighties (Damasio & Maurer, 1978; Vilensky, Damasio, & Maurer, 1981). Vilensky et al. documented gait disturbances in autistic and normal children. The investigators reported gaits in autistic subjects that were similar to those seen in Parkinsonian adults – particularly, a slower walk than normal with shorter steps. They suggest that the autistic syndrome might be associated with specific motor system dysfunction affecting among other structures the basal ganglia (Vilensky et al., 1981). These findings failed to generate much interest in the scientific community at the time probably because it was difficult to fit these results into the understanding of autism that existed then (Leary & Hill, 1996).

In accordance with Vilensky’s findings on a Parkinsonian-like gait in autistic children, Courchesne and colleagues have used MRI techniques to show abnormally developed cerebellar vermis (Courchesne et al., 1994). The cerebellum plays a crucial role in the integrative control of locomotion and is an integration center for information from higher and lower brain centres (Ganong, 2001). Further kinematic gait and neuroimaging techniques are required in order to fully assess the relationship between the two.

In their exploratory analysis on movement disturbance in autism, Leary and Hill advocate the re-evaluation of earlier investigations on the topic of movement disturbances in ASD. They suggest that motor disturbances might be symptomatic of the distinct behaviors that occur in ASD, providing a useful perspective form which to evaluate the disorders (Brasic, 1999; Leary & Hill, 1996; Willemsen-Swinkels & Buitelaar, 2002).

More recently, attention has been focused on the possible motor system dysfunction in individuals with ASD and its association with the core features of these disorders (Leary & Hill, 1996; Nayate et al., 2005; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998). Retrospective studies on children diagnosed with autism show abnormal motor development such as abnormal gait sequencing, delayed development through the stages of walking and abnormal hand positioning. These movement disturbances are thought to be present at birth suggesting that movement disturbances may be an intrinsic part of autism and underlie the core features of this disorder. The occurrence in the progression of these disorders is controversial. Current classifications of ASD fail to include descriptions of motor disturbance symptoms in children with ASD (DSM-IV-TR, 2000). However, within recent years, more attention has been focused on the possible association between motor system dysfunction and the core features of autism.
of characteristic movement disturbances might be useful in the early detection of ASDs before social and linguistic difficulties manifest, providing some basis for the use of early interventional therapies (Teitelbaum et al., 1998).

**Future Considerations of DBS Application in Autism Spectrum Disorder**

The application of DBS to PD has revolutionized the treatment of patients with advanced and/or drug resistant PD. The application of this therapy to conditions outside the movement disorder spectrum holds great promise. However, the optimization and application of this therapy to treat other disorders such as ASDs will rely on the full elucidation of the mechanisms involved in DBS action. In addition, a better understanding of the mechanisms underlying the core features of ASDs, in particular, the role that epilepsy and epileptiform activity play in the language and social regression in individuals with ASD is needed. Future application of DBS technology in ASD will also depend on the development of an appropriate experimental animal model of ASDs and addressing several important neuroethical considerations.

**Animal Models of Autism Spectrum Disorders**

The complexity and heterogeneity of symptoms in individuals with ASD makes it particularly difficult to define a neurological mechanism that underlies the core features of ASDs. To date, there is no consensus about the mechanisms involved in the neuropathology of these disorders (Tuchman & Rapin, 2002). However, postmortem and imaging techniques have provided some indication of the brain structures implicated in the progression of these disorders. These studies indicate subtle cellular maldevelopment of the brain rather than destructive lesions. The affected areas include the cerebellum, limbic system neocortex, amygdala, frontal lobe, and the temporal lobe including the hippocampus. However, the abnormalities that have been found are quite diverse and based only on small sample populations comprised mostly of adults rather than children (Bauman & Kemper, 2005; Nayate et al., 2005; Spence, Sharifi, & Wiznitzer, 2004; Tuchman & Rapin, 2002; Willemsen-Swinkels & Buitelaar, 2002).

Efforts to identify a neurochemical substrate in the ASD brain have been challenged by several factors including the lack of a suitable animal model (Bauman & Kemper, 2005). Sereotonergic, dopaminergic and histaminergic signaling systems have been theorized to be involved in the pathophysiology of ASD (Di Martino & Tuchman, 2001). In a study that assessed the effects of low-dose levodopa therapy in twenty children no significant treatment
effect was reported; however, 20% of children had improved outcomes (Sugiyama, Sugie, Igarashi, Ito, & Fukuda, 1998).

Though there is an urgent need to generate animal models to investigate several questions that human autopsy material has failed to address, however, no suitable model currently exists. The main challenge to the development of animal models for ASD is the strict diagnostic criteria of these disorders. ASDs are strictly classified as socio-behavioral disorders with clinical features that are almost impossible to replicate in a model organisms (Moy, Nadler, Magnuson, & Crawley, 2006).

**Patient Selection**

The diagnosis of ASD or PDD are based on the definitions provided by the tenth revision of the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association 4th edition (DSM-IV-TR) (1992; 2000). Children with ASD are generally diagnosed by the age of three years; however, despite the recognized reliability and validity of the most recently revised DSM-IV-TR and ICD-10 definitions of ASD, assigning a diagnosis is complicated. The identification of ASD affected individuals is challenged by several factors including mistaking non-diagnostic behaviors for diagnostic ones. Furthermore, to be noted is that quite a number of well-studied genetic disorders can mask as ASD, including fragile X syndrome, phenylketonuria, neurofibromatosis and others (Joshi, Percy, & Brown, 2002).

The challenges encountered in diagnosing ASDs may originate in the current diagnostic criteria employed. The existing definitions focus on social and behavioral facets and fail to consider coexisting symptoms such as motor disturbances and epilepsy/epileptic activity. Researchers have shown that when movement is analyzed in infants ASDs can be diagnosed from as early as 4-6 months and even as early as birth (Teitelbaum et al., 1998).

For the selection of a potential patient population for the application of DBS in ASDs, several important considerations must be made. Firstly, the potential subgroup should be a well defined group of individuals with ASD who present with common clinical symptoms. These symptoms should probably include those that have been successfully treated with DBS technology such as characteristic movement disturbances and distinct EEG profiles and epilepsy. Tentative targets could be similar to those in epileptic patients and could also include structures of the limbic system but would depend on more in depth understanding of the pathophysiology of ASDs.
The second important consideration is the age range of the patients. Early intervention and treatment of the clinical symptoms of any disorder usually always leads to better management, outcome, and quality of life for the affected patient. ASDs are no exception and with the use of DBS technology in these disorders, the early application of this therapy may be particularly important if epilepsy and epileptic activity actually contribute to the decline in cognition, language and behavior. However, defining a suitable age range for a potential patient population, will depend on how well tolerated the procedure is in young infants. In addition, the cognitive function of the patient population is an important consideration as cognitive impairment is a contraindication for DBS. Nevertheless, VNS has been successfully used to treat epilepsy in infants as young as eleven months old (Patwardhan, Stong, Bebin, Mathisen, & Grabb, 2000).

**Neuroethics**

Neuroethics is an emerging field that assesses the risk-benefit ratios involved in modern research on the brain in addition to the social, legal or ethical implications of treating or manipulating the mind (Moreno, 2003). Estimated risks associated with the immediate complications of DBS are approximately 5% (Lozano & Hamani, 2004; Theodore & Fisher, 2004). In a recent review on bilateral STN stimulation for PD, estimated adverse effects related to stimulation were 19% (Hamani, Richter, Schwalb, & Lozano, 2005b). These effects could be reversed with adjustment of stimulation parameters. The incidence of severe side effects such as death or permanent neurological deficits was reported to be between 1-2% however, adverse side effects such as infections and hardware problems were 9% (Hamani et al., 2005b). As far long term complications are concerned, important factors related to the damage of brain tissue have not been clearly defined (Lozano & Hamani, 2004; Theodore & Fisher, 2004). These factors include the type of electrode (platinum vs. steel) and the stimulus parameters (charge and current density, stimulus and pulse duration) (Siegfried, Lazorthes, & Sedan, 1980).

Other ethically related issues include the long term effect of electrical stimulation on brain tissue, particularly neurotransmitter systems. In addition, other concerns are associated with the permanence in position of these electrodes in the long term as well as in the event of head injury and how a change in position could affect brain activity (Siegfried, Lazorthes, & Sedan, 1980). More specific concerns about the potential use of DBS in ASD affected children are related to the long-term effects of electrical stimulation on the growing and developing brain.
Conclusion

Deep-brain stimulation is now considered the most effective neurosurgical therapy for movement disorders. The therapeutic effect of applying this technology in PD patients may be paralleled in epileptic patients; however, this effect awaits confirmatory studies. Thousands of epileptic patients that do not respond to or are ineligible for conventional treatment stand to benefit from the potential beneficial effects of DBS technology. More importantly the population of epilepsy patients that have other underlying medical conditions such as ASD may be able to experience significant improvements in the quality of their life and/or the progression of their disease.

There are currently more than 100,000 Canadians living with autism and there are indications that this number is increasing. Some Canadian provinces show increases of more than 63% within the last two years (Dakin, 2003). Authorities suggest that the reported increase is due to the increased recognition and revisions of the diagnostic criteria. However, these explanations are not thought to fully account for the documented trends in ASD prevalence (Trevathan, 2004).

The future consideration of DBS technology in ASD requires a shift in the way that these disorders have been classically viewed diagnosed and treated. A symptomatic approach to ASD assessments may facilitate the characterization of particular movement disturbances in these disorders. This might be useful in characterizing the core deficits of the heterogeneous group of ASDs thereby facilitating optimal therapeutic options for affected persons. Despite the possibly diverse neurochemical and/or neurological pathophysiology of ASDs, there may be a particular subset of individuals with ASD that present with common definitive and measurable features. These features may be co-existing epileptiform activity with or without epileptic seizures and movement disorders indicative of basal ganglia dysfunction. This subpopulation of individuals with ASD might represent a significant proportion of individuals on the most severe end of the autism spectrum.

The potential benefit for these patients with DBS technology may be twofold. While preventing the debilitating effects of epileptic seizures and self-injurious behavior, it may slow or prevent regression in these individuals. The potential improvement in their quality of life with the application of DBS technology warrants the consideration of investigative studies into the efficacy of its future use.
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