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Towards understanding the comorbidity of Functional Neurological Disorder in epilepsy

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Abstract

Epilepsy has a well-established connection with many comorbid disorders, including depression, neuropathic pain, psychosis, anxiety, and schizophrenia. In particular, a correlation between epilepsy and Functional Neurological Disorder (FND) is emerging. In this paper, a possible explanation for FND arising as a comorbidity of epilepsy is explored. Seizures have long been known to alter brain function. Excitotoxic damage has proven to be a likely candidate for the causation of some of the previously listed comorbidities. Specifically, seizure-induced alterations of gamma-aminobutyric acid (GABA), a primarily inhibitory neurotransmitter, may be implicated in the development of this disorder. GABA affects – and is affected by - other neurotransmitters such as dopamine and cortisol, both of which may play roles in developing the disorder and cementing FND-related neural pathways. Disruption of the inhibitory/excitatory balance between GABA and glutamate has previously been implicated in movement disorders and motor tics. Such disorders have a particular relation to structures of the basal ganglia. Injections of GABA antagonists into particular areas of the basal ganglia can cause decreased binding at GABA receptors and elicit motor tics. Therefore, seizure-related alteration of GABA function in these structures may provide a mechanism for the development of FND in epileptic patients. Furthermore, the altered function of these receptors could provide a role for anti-epileptic drugs (AEDs) in catalyzing this disorder. Seizure-induced alterations in the brain may have the capacity to induce FND, and AEDs may exacerbate or catalyze this disorder. It is often assumed that FND symptoms arise due to stress. This review will also explore why this may not always be the case.

Keywords

Epilepsy, Functional Neurological Disorder, Comorbidity, Basal ganglia, GABA, Inhibitory/Excitatory, Anti-epileptic drugs, Seizure, Glutamate, Dopamine

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Introduction

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, Functional Neurological Disorder (FND) is defined as the presence of one or more symptoms of altered voluntary or sensory function, with clinical findings showing the symptoms to be incompatible with recognized neurological or medical conditions (1). One of the greatest established risk factors is stress (2); consequently, FND often falls into the space between neurology and psychology, and therefore receives little attention. Furthermore, causes outside of excessive stress, post-traumatic stress disorder (PTSD), childhood trauma, and propensity to anxiety are rarely considered. FND symptoms can differ from case to case, presenting with neurological symptoms including but not limited to dissociative seizures, dystonic posturing, paralytic episodes, tic-like movements, abnormal gait, sensory issues, and myoclonic jerks. Depending on the severity, FND can have a significant impact on quality of life, and therefore deserves greater attention from the medical community.

The body of research on the mechanisms behind symptoms is limited; however, the disorder has been related to alterations in white matter and gray matter (3,4). Specifically, in patients with FND, a lower volume of the left sensorimotor cortex was observed, whereas a greater gray matter volume was observed in the left amygdala, left putamen, left caudate nucleus, left cerebellum, left parahippocampal gyrus, and bilateral thalami. There was also a greater volume of the left striatum (5), indicating alteration of these structures in FND. FND has also been linked to differences in white matter, including a loss of integrity in the stria terminalis/fornix, medial forebrain bundle, extreme capsule, uncinate fasciculus, cingulum bundle, corpus callosum, as well as changes in projections from the striatum to the postcentral gyrus (4).

Dysregulation within neurotransmitter systems have also shown correlations with FND. A study to test dopamine's role in reward error prediction found that dopaminergic neurons fire when learning a reward association, but stop firing once the association is fully learned (6). The contemporary motor model predicts that motor action follows a feed-forward model of sensory prediction of movement. Therefore, an error in this system may lead to functional symptoms (7). Another study found connections between dopaminergic dysregulation and FND, predicting that alterations in dopaminergic neurons in the periaqueductal gray matter could be a potential cause for the development of FND (8). This was supported by functional magnetic resonance imaging studies showing increased functional connectivity between emotional and motor control circuits in patients with FND (9). In particular, these studies highlighted the previously established link between dopaminergic projecting in pathways involving the hippocampus and cerebral cortex projecting to the basolateral amygdala and then to the dorsal and ventral striatum. They also identified a pathway involving the central nucleus of the amygdala and terminal striae of the basilar nucleus, receiving projections from the basolateral amygdala, and then projecting to gray matter. These data suggest motor control circuit dysfunction and errors in reward prediction as a possible mechanism for the development of FND (8). This hypothesis supports associations between FND and high

levels of stress, childhood trauma, propensity to anxiety, or PTSD. However, there has not been a conclusively accepted model for the pathophysiology of FND, and therefore, additional research is needed to examine current and future proposals for the pathophysiology of the disorder.

Discussion

Excitotoxic damage

Prolonged or frequent seizures have been associated with elevated glutamate levels, which can lead to neuronal death or damage. Chronic seizures are known to cause changes in the expression of glutamate receptors and uptake transmitters which can contribute to epileptogenesis (10). Further, repeated synaptic activation is associated with the triggering of rapid Immediate Early Gene (IEG) synthesis. These genes are implicated in neuronal plasticity as well as synaptogenesis (11), making their activation a possible mechanism in the development of comorbid disorders following status epilepticus or chronic seizures. In comorbidities such as neuropathic pain, the dysregulation of IEGs is highly maintained (12). Glutamatergic excitotoxicity can lead to long-term changes in activity-dependent IEG expression (10).

Furthermore, ictal activity is associated with alterations in protein expression in the brain. Mesial temporal lobe epilepsy results in an up-regulation of the proteins DJ-1, SPR, BASP1, α-Inx, AADC, CLCA, and CLCB in the right hippocampus, which are all related to dopamine synthesis. However, an overall decrease was observed in DJ-1, SPR, AADC, β-synuclein, BASP1, CLCA, CLCB, SNAP25, α-Inx, and STMN1, all of which are involved in dopaminergic pathways (13). This alteration in dopaminergic networks following seizures may provide a new mechanism for instigating FND. Somatostatin, a neurotransmitter found in GABAergic neurons in the dentate gyrus, is critical to the function of this structure. However, its levels are very sensitive to excitotoxicity. The dentate gyrus plays a critical role in the regulation of inhibitory/excitatory networks in the hippocampus and how the hippocampus influences the limbic system (14). This implies that seizure-induced alterations in somatostatin in the dentate gyrus may disrupt GABAergic and glutamatergic regulation, thereby predisposing epileptic patients to FND.

Seizures have also been linked to alterations in the way the brain processes cortisol; moreover, elevated levels of cortisol are a proposed trigger for FND symptoms. Studies done on mice show that pilocarpine-induced seizures create profound alterations in the brain circuits responsible for stress reactivity, thus leading to sharply elevated glucocorticoid levels following even minor stress. This is connected to increased rates of anxiety and depression in people with epilepsy. Both stress and seizures are capable of modifying cortisol levels (15). Using neuroimaging, stress has also been linked to higher activation in the basal ganglia structures such as the ventral striatum and the left insula/putamen in women and the prefrontal and the orbitofrontal cortex in men (16). Furthermore, elevated levels of cortisol as a response to stress have been linked to the deactivation of certain structures of the limbic system, including the hippocampus, hypothalamus, medio-orbitofrontal cortex, and anterior cingulate cortex (17). Given that both stress and seizures have the capacity to alter

function in the brain, they may both provide a mechanism for the development of functional neurological disorders.

GABA receptors and subunits

GABA is the primary inhibitory transmitter in the brain, and along with glutamate, plays a prominent role in the pathology of epilepsy (18). GABA analogues have been used to identify three primary types of GABA receptors: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ receptors can be modulated by benzodiazepines, barbiturates, and steroids as well as selectively blocked by bicuculine. They are anion selective, leading subunits to generate a hyperpolarizing current of Cl^- when activated, generally decreasing excitability (19). $GABA_B$ receptors respond to baclofen and CCGP27492 with a selective upregulation in activity and respond to phaclofen with a selective decrease in activity. They are metabotropic receptors that activate to rectify K^+ gradients as well as inhibit high voltage activated Ca^{2+} ion channels (20). $GABA_C$ receptors respond only to certain GABA analogues in a folded conformation. A methylphosphonic acid analogue in a partially folded configuration selectively antagonizes these receptors (21). In contrast to both $GABA_A$ and $GABA_B$ receptors, $GABA_C$ receptors have been a target for any current AEDs, AEDs in development, or proposed medications.

Of these receptors, $GABA_A$ functions as the primary target for most AEDs. They work through five different subunits per receptor. The various subunits include six α (α1 to α6), four β (β1 to β4), three γ (γ1 to γ3), one δ, one ε, one θ, one π, and three ρ (ρ1 to ρ3), comprising twenty different subunits (19). Depending on both location and arrangement of these receptors, they may exert inhibition phasically and/or tonically. Arrangements located extra-synaptically primarily inhibit tonically whereas those located synaptically inhibit phasically. Different configurations can come together to alter the kinetics, pharmacology, trafficking, and location of the receptor (22).

$GABA_B$ receptors, as previously mentioned, modulate K^+ and Ca^{2+} gradients. At presynaptic terminals, $GABA_B$ receptors work to mitigate excitability by suppressing Ca^{2+} currents and at postsynaptic neurons to increase K^+ conduction (23). Antagonists of $GABA_B$ receptors can block both typical and atypical absence seizures while agonists can exacerbate them (24).

Basal ganglia function and its implication in movement disorders

The basal ganglia are a collection of subcortical nuclei in the cerebral hemispheres consisting of the corpus striatum and globus pallidus (25). The striatum contains the lenticular (putamen and globus pallidus) and caudate nuclei, subthalamic nucleus (STN), and substantia nigra. Notably, the substantia nigra is a critical midbrain site for GABA mediated inhibition of seizures (26). The limbic and prefrontal regions of the thalamus and cortex both receive projections from the basal ganglia. These regions also manifest reward and aversion emotional processing and executive decision-making in a similar manner to the basal ganglia (27). The basal ganglia can be thought of as a circuit board, forming connections with separate areas of the brain. It is a key part of a network in control of motor function, filtering out unwanted or faulty signals. Though the basal ganglia are primarily involved in motor

function, they play important roles in motor learning, executive functions, behavior, and emotion (28). The networks in control of processing senses, namely those of sight, smell, taste, touch, and sound, also send input to the basal ganglia (29). A dysfunction in this area of the brain may also explain sensitivities to certain sensations in patients with FND or tic disorders, such as non-epileptic seizures induced by loud noises. Proper functioning of the basal ganglia requires dopamine release at input nuclei. Consequently, dysfunction of the dopaminergic pathways in the basal ganglia is implicated in several movement disorders including Parkinson's Disease, dystonia, chorea, and Tourette's Syndrome (28). These disorders are often associated with structural alterations within the basal ganglia. For example, in Tourette's patients, an imbalance exists between inhibitory receptors in the striatum and the internal segment of the globus pallidus (GPi), indicating a malfunction of the cortico-striato-thalamic circuit in severe cases. It is thus hypothesized that tics may result from local tonic inhibition in the striatum (30). A model proposing that Tourette's syndrome results from dysfunction of GABAergic circuits in the basal ganglia is supported by these findings (31), and given similarities between certain FND and Tourette's symptoms, these circuits are likely altered in FND as well.

Tonically Active Neurons (TANs) and Fast Spiking Interneurons are under dopaminergic control. These neurons are both used in the formation of complex microcircuits within the striatum. Given that over 90% of neurons in the striatum are Medium Spiny Neurons (MSNs), and all MSNs in the striatum are inhibitory and use GABA as their primary neurotransmitter (28), the striatum is an important area that may be implicated in movement disorders induced by GABAergic irregularities. Striatofugal neurons can be further classified as those sending input to the external segment of the globus pallidus (GPe) and those stimulating the GPi. Those providing input to the GPe express a dopamine receptor subtype 2 (D_2R), which inhibits adenylyl-cyclase, thereby creating an indirect inhibitory pathway. The MSNs providing input to the GPi and substantia nigra pars reticulata (SNr) possess dopamine subtype 1 receptors (D_1R) which inhibit adenylyl-cyclase, creating a direct stimulatory pathway (28,32). This finding is supported by studies showing that selective stimulation of MSNs expressing each of these dopaminergic receptors can provoke and arrest movement (33). In addition, lowering dopaminergic levels limits stimulation of direct pathway MSNs, thereby facilitating activity in the indirect circuit and in the STN. This may lead to increased output of neurons in the GPi/SNr. Similarly, the diminished GABAergic action along the direct pathway may further contribute to increased activity in the GPi/SNr (28). Although this model simplifies several of the biologically relevant signaling pathways, it is useful in providing a global framework to further explore altered firing patterns in the brain, since any alterations of either pathway may be of note in movement disorders (34). For example, studies on monkeys have shown evidence of dyskinetic states induced according to this model of decreased GPi output (35). This is functionally the opposite of the Parkinson's disease state, though this state was also associated with dyskinesia and chorea (36,37). Taken together, these data may indicate that functional symptoms can arise *via* different forms of dysregulation in these pathways. Dopaminergic signaling is also

linked to motor learning and habit formation (28). Furthermore, the ability to synthesize dopamine operates in synchrony with inhibitory activity in the caudate nucleus, which is regulated by striatal glutamate levels (38). Therefore, seizure-induced glutamate elevations in the striatum could alter dopaminergic function in a manner that could alter motor learning leading to the presentation of functional symptoms.

The cerebral cortex provides glutamatergic input to the STN through what is known as the hyperdirect pathway (39-41). This pathway plays an important role in the functioning of the basal ganglia (41). Direct projections from the cerebral cortex to the STN stimulate output nuclei allowing motor-related cortical areas a way to bypass input nuclei. This is associated with shorter signaling times than the indirect and direct pathways through the basal ganglia. Cortical inputs from the primary motor cortex and the supplementary motor area, premotor cortices, and certain visual field areas are conveyed through this pathway and organized at the STN (41,42), which may implicate dysfunction of this pathway in FND. When pharmacologically stimulated with inhibitory or excitatory medications *via* microinjection in the parafascicular nucleus, opposing changes were observed in the ipsi- and contralateral STN. This suggests the critical role of the parafascicular nucleus in the bilateral regulation of the basal ganglia through the STN (43). Crossman et al. (44) proposed that the lateral section of the globus pallidus is responsible for the development of chorea (44), which has similarities to certain FND symptoms. This may implicate the globus pallidus in certain cases of the disorder. The caudate nucleus has been shown to have distinct zones of pharmacological immunoreactivity (45).

Striosomes - compartments in the striatum that are important to basal ganglia function - are characterized by a strong response to GABA levels along with enkephalin, substance P, and neurotensin (45,46). In women with mesial temporal lobe epilepsy, pro-enkephalin B was present as part of the epileptic pathology (47). This presence could lead to an increase in enkephalin levels, thereby altering striosome function. A response to GABA and enkephalin could characterize a role for striosomes in the development of FND. These structures receive input, mainly emotional, from the prefrontal cortex, the limbic system, and the amygdala. They are often situated next to TANs, which are involved in associating actions with rewards (48), working with the hypothesis of reward prediction error involved in FND. Their role in reward-prediction errors may indicate some involvement of TANs in the reinforcement of FND pathways in people presenting with a premonitory urge.

Movement disorders resulting from dysregulation of the excitatory/inhibitory balance

Patients with Tourette's syndrome have been shown to have higher levels of glutamate in the premotor cortex, the striatum, the dorsolateral prefrontal cortex, and the ventromedial prefrontal cortex, (49). Specific GABA inhibition in regions of the basal ganglia and its associated structures have also been linked to motor abnormalities. Bicuculline, a $GABA_A$ receptor antagonist, injected into the motor putamen led to tic-like focal muscle jerks that were accompanied by an elevation in GPe activity and a decrease in firing of the GPi

(which may also be correlated with increased action along the direct pathway), along with increased activity in the primary motor cortex (50). Notably, decreased function and binding at $GABA_A$ receptors has been reported in epilepsy (51). This suggests that movement corresponds with a reduction of GPi output activity in a time-related fashion (28). Focal bicuculline injections blocking specific subregions of the striatum, GPe, and STN elicited dyskinesias along with other abnormalities when injections were focused at the motor, limbic, and associative regions (52,53). Primates, rats, and mice have all been used to demonstrate that an imbalance between glutamate and GABA levels in the striatum leads to tic-like symptoms (54). In patients with schizophrenia, some of the alterations in white matter are attributed to low levels of GABA (55), and a similar mechanism may explain some of the alterations of white matter seen in FND patients.

Worbe et al. (31) found that 40% of bicuculline injections into the dorsal anterior striatum elicited these symptoms, making it likely that this area can be implicated in FND (31). Different areas of the striatum, when injected with bicuculline, elicited different dyskinetic behaviors (56), indicating that different areas of the striatum may be altered in different ways for FND patients presenting with different symptoms. Furthermore, neuroimaging has shown activation of the anterior striatum, motor cortex, insula, and cerebellum during tics (57). The strong activation of the cerebellum and insula implicates them in tic initiation and execution (58). As certain functional symptoms are comparable in presentation to tics in Tourette's syndrome, these brain structures may be involved in the determination of the pathophysiology of FND. The anterior striatum region receives input from primary and supplementary motor areas (59-61) as well as the premotor cortex, dorsolateral, and parietal cortices (62,63). As a result, this area is likely implicated in motor learning (31). Electrophysiological and neuroimaging studies show that the caudate nucleus is involved in movement selection, the anterior putamen plays a role in the preparation of movements, and the posterior putamen is activated during movement execution (64). These areas may all have important implications for FND, but given the excess activity observed in people with tics, an issue with motor selection may similarly be implicated in FND. Studies showing excessive activation of the supplementary motor cortex during tics, but not before, and only slight activity in the premotor cortex, seem to affirm the spontaneous nature of tics (65). This model may confirm the involuntary nature of functional symptoms as well, since a similar pathology may exist in both disorders.

Given the diverse nature of symptoms in FND, it is not unreasonable to assume that a perturbation in the anterior striatum may not only lead to functional tics, but also symptoms such as paralysis, gait disorders, and non-epileptic seizure activity. As both status epilepticus and chronic epilepsy are known to lead to significant alterations in GABA and glutamate levels, exceptionally long status epilepticus and/or periods of chronic seizures may therefore also result in FND symptoms, given their capability to disrupt the balance between these two chemicals.

Homeostasis of the excitatory *vs.* inhibitory balance is key in maintaining synaptic integrity; consequently, there are several

mechanisms in place to maintain this homeostasis by regulating synaptic and circuit activity (66). This often involves selective excitatory and inhibitory alterations such as plasticity in pre- and postsynaptic excitatory synaptic plasticity (67). When glutamate receptors' functioning is impaired, this may lead to compensatory release of glutamate to restore appropriate levels (68). When there is a pharmacological blockade of postsynaptic glutamate receptors, over-compensation can quickly occur, and these levels become very sensitive to even small changes in the amplitude of excitatory postsynaptic potentials (66).

Alterations in GABAergic systems following seizures

Seizures may also lead to damage of GABAergic receptors, which is commonly associated with a down-regulation of GABA following seizures due to run-down and neuronal death, a proposed mechanism for the development of epileptogenesis. However, there is also evidence for a compensatory increase in GABA levels (69). *In vitro* evidence has shown that $GABA_B$ receptors are necessary for proper homeostatic function in the hippocampus (70). A long-term compensatory increase in $GABA_B$ receptors was observed in mice following prolonged seizures, another mechanism by which inhibitory activity may increase following an epileptic seizure (71). However, this upregulation of inhibition may lead to functional disconnection of GABAergic synapses that can contribute to hyperexcitability (72). Despite compensatory increases in GABAergic activity, significant damage to $GABA_A$ receptors can occur following seizures. This can lead to significant alterations in responses to certain medications and drugs (69).

Brodie et al. (73) proposed that damage to GABAergic neurons can lead some of these neurons to respond to an agonist by a decrease in activity (73). A study by Dubanet et al. (74) tested this effect in the hippocampus *in vivo*, finding that an excitatory shift occurred only in a minority of neurons in a minority of mice. They found that out of 23 mice, only three showed an excitatory shift in GABAergic neurons, and of those three, only four of their putative pyramidal neurons out of the 78 neurons examined exhibited this switch, for a 0.6% global incidence. Although this is a low probability, the authors still promote the possibility of alterations in other brain areas (74). Given that striosomes are extremely sensitive to GABA levels, the possibility of a switch in the polarity of $GABA_A$ receptors inducing a functional disorder cannot be discounted. However, the most striking finding of the study was a loss of inhibitory control of pyramidal neurons (74). This may play a role in alterations in the development of action potentials of these neurons and executive motor function and therefore development of FND circuits. The study attributed the depolarizing action of GABA to altered Cl^- gradients following seizures which may contribute to run-down of these receptors. Fluctuations in this gradient contribute to normal fluctuations of GABA as an excitatory *vs.* inhibitory neurotransmitter. The group observed this through the measurement of field-inhibitory postsynaptic potentials (fIPSPs), reversed polarity in fIPSPs being associated with reversed GABAergic polarity. A week after the mice were originally treated with kainic acid, pyramidal neurons were no longer under

GABAergic control. This more gradual effect serves as a model for alterations linked to epileptogenesis in chronic epilepsy. Furthermore, in acute seizures, a time-locked relationship between seizures and GABAergic excitation was found in the hippocampus, with no fIPSP-related excitatory action after the normal polarity of the fIPSPs was restored (74). However, this study was limited to hippocampal alterations following ictal seizures, and it is therefore limited in scope. Huberfield et al. (75) found that ~20% of GABAergic neurons in the subiculum depolarized to excitatory potentials in temporal lobe epilepsy. They found a decrease in KCC2 mRNA expressed in the dentate gyrus following pilocarpine-induced seizures *in vitro* (75). There is also evidence for long-term rearrangement of glutamatergic networks and depolarization in GABA following status epilepticus, a likely mechanism for epileptogenesis leading to chronic seizures (75). The similarities between the chronic stress and epilepsy models provide important parallels between the development of FND as a result of stress and FND as a result of epileptic seizures.

Such alterations in GABAergic systems could quite possibly explain the emergence of functional symptoms following status epilepticus or chronic seizures. Given the ability of $GABA_A$ antagonists to induce movements akin to motor tics, depolarization of GABA receptors is likely to have a similar effect, particularly if these alterations extend to areas of the basal ganglia previously implicated in eliciting these movements. Unfortunately, only a limited body of research exists on the alterations of GABA receptors resulting from seizures, and the vast majority of it is limited to the hippocampus. Furthermore, a possible shift of GABA to an excitatory transmitter has important implications with regard to responsiveness to medication, epileptogenesis, and the development of comorbidities. However, *in vivo* studies on alterations in GABAergic alterations have faced difficulties in that recording methods and activation of GABAergic transmission are both key and prone to variability. Patch clamp (cell-attached) recordings to gain information from one neuron at a time may also disrupt neuronal and channel dynamics (77), and transmission may be altered as a result of normal shifts in the Cl^- gradient (74). Alterations in GABA are not only necessary to understanding comorbid functional movement disorders of epilepsy, but are also key to understanding of other epileptic comorbidities, epileptogenesis, the development of chronic epilepsy, and medication response. As such, further research on alterations of GABA receptors following seizures is of utmost importance.

The possible role of medication in the development of FND

Given that many AEDs modulate the glutamatergic and GABAergic systems to regulate epileptiform activity, many may be involved in the development of movement disorders. For example, topiramate, levetiracetam (78), tiagabine, valproate, and vigabatrin (79) are all known to modulate the GABAergic and glutamatergic systems in some way. Ganaxalone, cenobamate, and diagabine are all recently developed drugs, or in clinical trials, that are also known to modulate these pathways (22,80). Given that pharmacological disruption of glutamate can lead to rapid overcompensation in the production of this neurotransmitter, drugs that act on glutamate

and GABA are prime candidates for the initiation of movement disorders. In particular those that act as an antagonist of the N-methyl-D-aspartate (NMDA) receptor or other postsynaptic glutamate receptors as well, would likely lead to the compensatory increase outlined by previous studies (66), thus making them of special importance in examining the safest AEDs for epileptic patients with FND. Combined with the possibility that excitotoxic damage may lead to significantly altered functioning of $GABA_A$ receptors (73), the anti-epileptic action of agonizing GABA receptors could lead to decreased $GABA_A$ receptor binding (73) and therefore could catalyze FND development in epileptic patients. This could create conditions similar to those induced by bicuculline injections shown to cause motor tics. The existing disruption in GABA and glutamate levels in the brain resulting from chronic or prolonged epileptic seizures may lead to the homeostatic mechanisms in the brain losing the ability to compensate appropriately to pharmacological alterations in the levels of neurotransmitters. This may occur when the significant alterations induced by seizures are not enough to cause the development of functional movement disorders on their own. Furthermore, slight alterations in these levels following changes in anti-epileptic medication may also increased disruption of this balance, thereby inducing functional symptoms. Further research is needed to isolate how specific drugs may affect the GABAergic and glutamatergic systems in both epileptic and non-epileptic patients.

Given its wide use as an AED, levetiracetam (LEV) is of special interest. It is an NMDA antagonist, which is a proposed mechanism for its side effects of rage and depression (78). This may implicate it in leading to a rapid compensatory increase in glutamate levels which is an associated mechanism of movement disorders. However, LEV is considered a $GABA_A$ agonist. Nevertheless, in cases that include damage to $GABA_A$ receptors significant enough to lead to altered function, LEV may exacerbate the imbalance in the striatum induced seizures. Alteration in striatal dopaminergic function can result from glutamatergic dysregulation in the prefrontal cortex, which is another mechanism by which functional symptoms could arise in patients (3,81). The development of these disorders as a result of medication may be especially likely in the event of a medication change, given the compensatory levels of glutamate induced by certain drugs and the significant sensitivity that follows this disruption of homeostatic mechanisms (66).

Also widely used as AEDs, benzodiazepines are known for their agonization of $GABA_A$. They are often the first line of defense against status epilepticus. Many common emergency medications such as diazepam and clonazepam are benzodiazepines. However, due to altered physiology such as $GABA_A$ rundown during prolonged seizures, benzodiazepines may lose efficacy (82,83). They bind with at least three allosteric sites on the $GABA_A$ receptor. Benzodiazepine binding sites are located extracellularly. The third site is located on the transmembrane domain and is another allosteric site to which benzodiazepines may bind. Depending on the specific compound, benzodiazepines are active at different $GABA_A$ subunits (84). Mesial temporal lobe epilepsy is associated with a loss of benzodiazepine binding sites, decreasing the efficacy of many benzodiazepine treatments (85). A similar

effect is observed during prolonged seizures. This has inspired the creation of newer AEDs including darigabat and ganaxalone, which have been synthesized with the goal of being positive allosteric modulators with higher efficacy and a lower potential for side effects such as tolerance and addiction (80). During status epilepticus, synaptic $GABBA_A$ receptors internalize. Benzodiazepines bind only synaptically, therefore they lose efficacy during prolonged seizures (86).

Other drugs that work through GABAergic mechanisms may have similar potentials to exacerbate and/or catalyze FND. Topiramate is a 2nd generation AED and works by upregulating activity at the $GABA_A$ receptor, thereby increasing the inhibitory effect. It also downregulates activity at NMDA receptors, making it likely to cause a compensatory increase in glutamate, further disrupting the excitatory/inhibitory balance. Topiramate also blocks voltage gated sodium channels, establishing depolarization control during seizures (87). Given its common use, it is of particular interest in examining comorbid functional symptoms in epilepsy. Valproic Acid, another widely used AED, works by increasing the synthesis of glutamic acid decarboxylase (GAD), which is responsible for converting glutamate to GABA. Valproic Acid also works by increasing $GABA_A$ mediated inhibition (88). This suggests the possibility of the potential for antagonizing activity on $GABA_A$ receptors following seizure-induced shifts in polarity.

Recently developed drugs that act on the GABAergic system include darigabat, ganaxalone, cenobamate, and ENX-101. Since several of these act upon the $GABA_A$ receptors, they are notable when epileptic patients present comorbidly with FND. Darigabat resulted from the search for $GABA_A$ positive allosteric modulators that maintained the antiseizure and anxiolytic properties of benzodiazepines but reduced adverse effects such as tolerance, addiction, and cognitive dysfunction. It is an imidazopyridine derivative that is structurally different from benzodiazepines and neurosteroids (80). As examined *in vitro*, darigabat binds at $GABA_A$ receptors containing α1, α2, α3 or α5 subunits with a high affinity, but is unlikely to bind α4 or α6 subunit containing $GABA_A$ receptors, which lack a benzodiazepine binding site. Darigabat behaves pharmacologically as α2/3/5 subtype-selective, $GABA_A$-positive allosteric modulator of α1 subunits (89).

Ganaxolone is an allopregnanolone methyl analogue, formed by the addition of a methyl moiety position 3β of the steroid skeleton, which results in the compound being orally active. It is currently approved for seizure disorders related to CDKL5 deficiency disorder for patients two years of age or older in the USA (90). It binds both synaptically and extra synaptically. Benzodiazepines may lose efficacy during status epilepticus given they bind only to synaptic receptors, which internalize during prolonged seizures. However ganaxolone responsive extrasynaptic GABAA receptors containing α and δ subunits do not internalize, allowing ganaxolone to exert an anti-epileptic effect even during extended seizures (86). Interestingly, in kindling models, pilocarpine induced status epilepticus models, and 6 Hz models in mice, female animals were more responsive to the drug. This was attributed to greater concentration of extrasynaptic GABAA receptors containing the

δ subunit in female animals. However, there were no differences between sexes when the δ subunit was lacking (86).

Cenobamate is a carbamine derivative approved for treatment of focal seizures in adults by the US Food and Drug administration in 2019 (91) and for treatment of focal seizures in adults whose seizures were not controlled despite having been on at least two different medications (92). Cenobamate likely works through a dual mechanism of binding to both synaptic and extrasynaptic $GABA_A$ receptors regardless of α subunit composition, increasing both tonic and phasic GABA-mediated inhibition by positive allosteric modulation. Cenobamate's effects likely result from an interaction with modulatory sites independent of benzodiazepine binding sites (93).

ENX-101 was designed with the intent to reduce seizure activity while mitigating adverse effects such as sedation and tolerance. A phase II randomized, double blind, placebo controlled study is ongoing comparing two different doses of ENX-101 (15 mg daily and 30 mg daily) with a placebo. It is scheduled to end ~December of 2024. The study focuses on patients with focal epilepsy aged 18-75 who experience drug resistant symptoms despite taking 1-4 AEDs. ENX-101 will be given in conjunction to any current medications taken by subjects (94). ENX-101 is a positive allosteric modulator of $GABA_A$ receptors containing α2, α3 or α5 subunits. However, it has no positive allosteric activity at receptors containing α2, α3, and α5 subunits, but devoid of activity at α1 subunit-containing receptors (95).

When examining AEDs that may be implicated in exacerbation or catalysis of comorbidities such as FND, drugs such as LEV, topiramate, valproic acid, ganaxalone, cenobamate, dirigabat, and ENX-101 are of particular interest due to their mechanisms of modulating $GABA_A$ receptors. Drugs that modulate activity at the NMDA receptor, such as topiramate and LEV are of special interest due to the rapid overcompensation that may occur when homeostatic glutamatergic mechanisms are disrupted. As research on alternative anti-epileptic therapies intensifies, alternative treatments may yield AEDs that elicit fewer severe side effects such as FND.

Relationship between GABA, stress, and seizures

The stress response is mediated by the hypothalamic-pituitary-adrenal (HPA) axis and it is largely under GABAergic control (96). Furthermore, the upregulation of glutamic acid decarboxylase (GAD) in direct and multi-synaptic circuits is responsible for hippocampal control of the HPA axis (97). Stress leads to the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which then signals pituitary release of adrenocorticotropic hormone, instigating the release of cortisol from the adrenal gland. The HPA axis receives input from many brain regions, and these inputs ultimately act on CRH neurons in the paraventricular nucleus. Though CRH neurons receive inputs from many brain areas as well, they are largely mediated by GABA (98). Tetrahydrodeoxycorticosterone acts on the δ subunit of $GABA_A$ receptors to typically evoke GABA-induced inhibition on CRH neurons. A study found that following stress, GABA no longer inhibits CRH neurons. High stress levels lead to a collapse in the Cl^- gradient and in the

excitatory actions of GABA resulting from depolarization and dephosphorylation of KCC2 (96), a K^+ and Cl^- cotransporter responsible for maintaining a low Cl^- gradient (99). However, this depends on the phosphorylation state of Ser940 and surface expression of KCC2 levels, not total KCC2 levels. It also supports the role of $GABA_A$ δ subunit-containing receptors in the mediation of stress response, but there is likely an additional mechanism such as presynaptic changes in GABA action to CRH neurons that cause the excitatory actions of GABA on CRH (96).

Although some AEDs are known to lower cortisol levels, in the model of chronic epilepsy, these drugs may not prevent highly dysregulated cortisol levels. Epileptic patients are more likely to have reactivity to acute stress compared to healthy controls (15). High seizure frequency is also related to decreased functional connectivity in the brain. These findings suggest that epilepsy could be a model for chronic stress (100). Acute stress in non-epileptic patients led to GABA concentrations being reduced by 29% in the corpus striatum and a 32% decrease in GAD activity, likely indicating that chronic stress leads to compensatory changes in the GABAergic system (101). This may provide an important likeness between models of stress-induced FND and the proposed model of seizure-induced FND.

These changes may also be important in models of FND triggered by anti-epileptic drugs and epileptic seizures. Many medications act as GABA agonists, so it is possible that chronic seizures and particularly long status epilepticus seizures prime the brain for alterations in the action of $GABA_A$ receptors. Subsequently, if GABA depolarization and excitatory actions eventually restore themselves to normal levels, there is still the possibility that the brain has already established a significant enough response to these levels (inducing non-epileptic seizures similar to those induced in the bicuculline model), creating a pathway leading to FND symptoms. This pathway may then be triggered by any stress-induced alterations of $GABA_A$ receptor function, even if insignificant. Since seizure activity exerts a similar effect to $GABA_A$ receptors as bicuculline, such a pathophysiology is particularly important in the perpetuation of FND symptoms.

Proposed pathophysiology

Artificially induced alterations in the glutamate and GABA balance have been shown to lead to motor tics and dystonia in many animal models. Such an imbalance could also be provoked after a period of frequent or prolonged epileptic seizure activity. Altered plasticity resulting from higher IEG levels may also make patients with epilepsy more prone to the development of FND. Medication may also play a novel role in the exacerbation or catalysis of these disorders. It has previously been proposed that excitotoxic damage can significantly alter the function of GABAergic neurons and receptors such that agents that typically act as GABA agonists instead suppress GABAergic activity (73), which has been supported by studies highlighting the alteration of $GABA_A$ receptor function in certain areas of the brain. Changing anti-epileptic drugs that differentially modulate GABA may lead to further disruptions of the homeostatic compensatory mechanisms for inhibitory and excitatory circuits. Overwhelming homeostatic mechanisms for

the regulation of these circuits may thereby lead to an imbalance in neurotransmitter levels that could cause abnormal motor functions. Imbalances in GABAergic activity induced post-ictally *via* neuronal damage and compensatory increases in GABA levels, combined with an elevated level of glutamate-induced from seizures, may lead to motor tics as seen when artificially induced in animals. These glutamate levels may also alter dopaminergic actions in the brain, which has been previously proposed as a mechanism for the development of FND.

Furthermore, elevated glutamate levels have been associated with damage of the basal ganglia. The basal ganglia is an important structure in motor control, accepting appropriate signals and rejecting those deemed incorrect or faulty. Therefore, impairing its processing ability may lead to signals being inappropriately accepted and may lead to motor dysfunction including nonepileptic seizures, dystonic, paralytic, tic, or gait disturbances. Since the basal ganglia receives input from sensory stimuli, dysfunction of this area provides an explanation for functional mimicking of other disorders as well as sensory triggers for episodes. Additionally, the basal ganglia are dense in cortisol receptors, explaining previously proposed sensitivities to cortisol fluctuations in FND patients. Moreover, alterations in other brain areas may play an additional role. The loss of integrity in the stria terminalis/fornix may be of particular interest due to it being an important output of the amygdala and hippocampus, which are related to emotion and learning (3). This should be noted due to the connection between FND symptoms and emotional/stress-related triggers. Further, the decreased functional connectivity in the corpus callosum may be implicated in certain symptoms such as gait issues.

These factors, when taken together, suggest the probability that Functional Neurological Disorders can arise as a result of seizures and AEDs. Per the maxim of Hebbian plasticity, "what fires together, wires together," so frequent stimulation of motor pathways *via* medication or seizures can lead to the development of a chronic disorder. This stimulation may come through the inability to regain homeostatic levels of glutamate and GABA for a period significant enough to cement the functional alteration in the striatum, creating functional symptoms in the default pathway. Cortisol fluctuations and sensory stimulation may further cement these pathways, thus leading to an increase in symptoms.

Potentially novel therapies for the treatment of epilepsy: $GABA_B$ targeted AEDs

$GABA_B$ receptors have a long established association with absence seizures, both typical and atypical (24). Agonists of $GABA_B$ receptors exacerbate seizure frequency in genetic, pharmacologically induced, typical, and atypical models of absence epilepsy, while antagonists both mitigate seizure activity as well as the cognitive impairment that results from seizures (24). The opposite has been true for mouse models of convulsive generalized and focal epilepsy (102). This dichotomy arises from the involvement of thalamic circuitry in absence epilepsy. The hippocampal - thalamocortical circuitry underpins atypical absence epilepsy while the thalamocortical circuitry is associated with typical absence epilepsy (102). Thalamocortical networks in

both typical absence seizures and atypical absence seizures are mediated by low-voltage activated Ca^{2+} currents. The low-voltage activated channels are found in both the thalamus (103) and the frontal cortex (104). The $GABA_B$ mediated inhibition of the low-voltage activated channels yields activation Ca^{2+} currents in this channel, causing an excitatory effect (24). However, drugs targeting $GABA_B$ receptors have only been examined preclinically due to potential adverse effects.

Future research on drugs specifically targeted to the $GABA_B$ receptor is very pertinent because medications targeting this site may have potential to protect against the development of FND in patients experiencing frequent prolonged seizures as well as in lessening symptoms which are exacerbated by different anti-epileptic drugs. Specifically, in the light of wear down and potential shifts in the polarity of $GABA_A$ receptors resulting from seizures that may be associated with FND, investigation into medications that do not act upon the $GABA_A$ receptor may have a lower potential to exacerbate symptoms of movement disorders by antagonizing $GABA_A$ receptors following seizure-induced shifts in polarity. Baclofen, a medication currently used as an antispasmotic and often prescribed for multiple sclerosis (105), acts as an agonist of $GABA_B$ receptors, which could potentially exert an anti-epileptic effect in patients with generalized convulsive or focal epilepsy. However, in patients with absence epilepsy, cognitive impairment was observed as a result of baclofen treatment (24). This was not commonly the case in prescriptions of baclofen when used as an antispasmodic agent (106). There are currently no clinical trials considering baclofen as a treatment for any form of epilepsy. Several other related compounds, such as phaclofen, acting on the $GABA_B$ receptor have not been considered as a treatment of FND in current clinical trials.

Significantly more research is necessary in order to address gaps in the current understanding of $GABA_B$ modulators for epilepsy. Given the correlation between the two disorders as well as impaired quality of life resulting from both epilepsy and FND, AEDs acting through different mechanisms such as modulating the $GABA_B$ receptor may be less likely to worsen symptoms than AEDs modulating the $GABA_A$ receptor. Agonists of $GABA_A$ receptors such as bicuculine have been shown to elicit motor tics. As epileptic seizures may yield shifts in the polarity of $GABA_A$ receptors, drugs modulating that receptor may exacerbate symptoms of FND. Thus, AEDs working by other mechanisms are needed.

NRTX 1001

Other varieties of therapies with the potential to be safer for patients with FND are those that target the regeneration of the GABA pathway as a whole. NRTX 1001 is comprised of particular pallial-type lineage GABAergic post-mitotic interneurons derived from human pluripotent stem cells. They are designed as a one-time implant to increase release of GABA at the epileptic focus (80). It is designed as a treatment for drug resistant focal epilepsy, and preclinical trials have shown positive results, with roughly 75% of treated mice being seizure free compared to 8% of controls (107). NRTX 1001 has recently entered early clinical trials, and the first two patients showed a significant response with a >90% reduction in seizure activity following three and six months after implantation (108). The goal of NRTX 1001 is

to introduce cells that have the potential to heal inhibitory networks that have been damaged by seizures, thereby allowing for long term seizure reduction (109). Since this therapy works by repairing damaged networks, it is less likely to exacerbate the symptoms of FND. Other medications that modulate $GABA_A$ following a shift in polarity may exacerbate FND symptoms by antagonizing $GABA_A$. Therapies targeting the repair of these networks may also have the potential to alleviate certain FND symptoms that arise from $GABA_A$ antagonization by medication. This can be achieved by restoring the appropriate polarity of these networks. Although NRTX 1001 is a direct implant by injection, it has been well tolerated without adverse effects in trials (110). However, the possibility of adverse effects as the therapy gains wider use must be acknowledged, as is the case with any invasive brain drug delivery.

Future potential of therapies targeted to specific structures

The genetic, cellular, and structural makeup of both the human and the non-human primate brain was mapped recently. These cerebral atlases may provide the potential to develop therapies targeted to specific brain areas. This research is relatively recent and thus has not yet elicited the development of any such therapies (111). However, focus of research on different anti-epileptic therapies provides the intriguing possibility for drugs with increased efficacy in treating epilepsy with fewer side effects. Iadarola and Gale identified the substantia nigra as a critical site for GABA mediated inhibition of seizures (26). Targeting therapies to that specific structure may help reduce the development of severe adverse effects, potentially even FND.

Perspective and conclusion

There are currently very few studies *in vivo* that examine the potential depolarization and excitatory actions of GABA in epileptic patients. Of those studies, none of them assess GABAergic reversal potentials in the striatum or other regions of the basal ganglia. *In vitro* studies provide strong evidence for reversal potentials following seizures, but they also fail to assess structures of the basal ganglia. Currently, there is no conclusion on the exact mechanism for the development of FND in non-epileptic patients, and there has not yet been a connection drawn between seizure-induced alterations in the brain and FND in epileptic patients. FND can significantly affect quality of life, and therefore deserves more attention by the medical community.

Future research in this area needs to place an emphasis on GABAergic depolarization *in vivo*. Using fIPSPs as a tool for *in vivo* assessment of shifts in Cl^- gradients has successfully determined shifts in GABA function. However, detection of potential shifts *in vivo* using fIPSPs may be less accurate because of shifts in the Cl^- gradient caused by invasive probing mechanisms such as patch clamp methods. A similar challenge is encountered when measuring membrane potentials. Increasing the volume of literature based on studies with these methods will lead to a better understanding of the relationship between seizures and GABAergic reversal potentials.

Studies linking epilepsy and FND are lacking despite the two conditions often coexisting. Future studies should focus on the frequency and impact of this comorbidity. This should involve an assessment of the frequency of FND presenting in epileptic patients aiming to

identify any associations with seizure disorder, frequency, type, and length (including the presence or absence of status epilepticus and associated impacts). There also needs to be an assessment of the role of AEDs in FND. Altered function in brain structures may promote a mechanism for AEDs to help catalyze or worsen FND in epileptic patients, and therefore correlations between FND symptom severity, the type of AED being taken, and the AED's action on the brain should be researched and analyzed.

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Abbreviations

AED - Anti-epileptic drugs, CRH - Corticotropin-releasing hormone, D_1R - Dopamine type 1 receptor, D_2R - Dopamine type 2 receptors, FND - Functional Neurological Disorder, fIPSPs - Field-inhibitory postsynaptic potentials, GABA - Gamma-aminobutyric acid, GAD - glutamic acid decarboxylase, GPe - External segment of the globus pallidus, GPi - Internal segment of the globus pallidus, HPA axis - hypothalamic-pituitary-adrenal axis, IEG - Immediate Early Gene, LEV – Levetiracetam, MSNs - Medium Spiny Neurons, NMDA - N-methyl-D-aspartate, SNr - Substantia nigra pars reticula, STN - Subthalamic nucleus, TANs - Tonically Active Neurons

References

1. Voon V, Cavanna AE, Coburn K, Sampson S, Reeve A, LaFrance WC Jr, Functional Neuroanatomy and Neurophysiology of Functional Neurological Disorders (Conversion Disorder), J Neuropsychiatry Clin Neurosci. 28(3): 168-190, 2016, https://doi.org/10.1176/appi.neuropsych.14090217

2. Liang F, Xu Q, Jiang M, Feng R, Jiang S, Yuan B, et al., Emotion Induced Monoamine Neuromodulator Release Affects Functional Neurological Disorders. Frontiers in Cell and Developmental Biology. 9: 2021 https://doi.org/10.3389/fcell.2021.633048

3. Perez DL, Williams B, Matin N, LaFrance WC Jr, Costumero-Ramos V, Fricchione GL, et al., Corticolimbic Structural Alterations Linked to Health Status and Trait Anxiety in Functional Neurological Disorder. Journal of Neurology, Neurosurgery & Psychiatry 88:1052-1059, 2017, https://doi.org/10.1136/jnnp-2017-316359

4. White Matter is Altered in Functional Neurological Disorder. Massachusetts General Hospital, 2017, https://advances.massgeneral.org/neuro/journal.aspx?id=1455

5. Maurer CW, LaFaver K, Limachia GS, Capitan G, Ameli R, Sinclair S, et al., Gray Matter Differences in Patients with Functional Movement Disorders. Neurology, 91(20): e1870-e1879, 2018, https://doi.org/10.1212/wnl.0000000000006514

6. Schultz W, Dayan P, Montague PR, A Neural Substrate of Prediction and Reward. Science. 275:1593-1599, 1997, https://doi.org/10.1126/science.275.5306.1593

7. Voon V, Brezing C, Gallea C, Ameli R, Roelofs K, LaFrance WC Jr, et al., Emotional Stimuli and Motor Conversion Disorder. Brain. 133(pt 5): 1526-1536, 2010, https://doi.org/10.1093/brain/awq054

8. Zhengming H, The Aversion Function of the Limbic Dopaminergic Neurons and Their Roles in Functional Neurological Disorders. Frontiers in Cell and Developmental Biology. 9: 713762, 2021, https://doi.org/10.3389/fcell.2021.713762

9. Szaflarski JP, Allendorfer JB, Nenert R, Pati S, Thomas AE, Ver Hoef L, et al., Facial Emotion Processing in Patients with Seizure Disorders. Epilepsy Behav. 79: 193-204, 2018, https://doi.org/10.1016/j.yebeh.2017.12.004

10. Barker-Haliski M, White HS., Glutamatergic Mechanisms Associated with Seizures and Epilepsy. Cold Spring Harb Perspect Med. 5(8): a022863, 2015, https://doi.org/10.1101/cshperspect.a022863

11. Thomas AX, Brooks-Kayal AR, Excitation–Inhibition Epilepsies. Neural Circuit Development and Function in the Brain, Chapter 36, Academic Press, Pages 709-730, ISBN 9780123972675, 2013, https://doi.org/10.1016/B978-0-12-397267-5.00042-X.

12. Obara I, Goulding SP, Hu JH, Klugmann M, Worley PF, Szumlinski KK., Nerve Injury-Induced Changes in Homer/Glutamate Receptor Signaling Contribute to the Development and Maintenance of Neuropathic Pain. Pain. 154(10):1932-1945, 2013, https://doi.org/10.1016/j.pain.2013.03.035

13. Sadeghi L, Rizvanov AA, Salafutdinov II, Dabirmanesh B, Syyah M, Fathollahi Y, et al., Hippocampal Asymmetry: Differences in the Left and Right Hippocampus Proteome in the Rat Model of Temporal Lobe Epilepsy. J Proteomics. 10(154): 22-29, 2017, https://doi.org/10.1016/j.jprot.2016.11.023

14. do Canto AM, Donatti A, Geraldis JC, Godoi AB, da Fosa DC, Lopes-Cendes I, et al., Neuroproteomics in Epilepsy: What Do We Know so Far? Frontiers in Molecular Neuroscience. 13: 604158, 2021, https://doi.org/10.3389/fnmol.2020.604158

15. Cano-López I, González-Bono E, Cortisol Levels and Seizures in Adults with Epilepsy: A Aystematic Review. Neuroscience & Biobehavioral Reviews.103, 216-229, ISSN 0149-7634, 2019, https://doi.org/10.1016/j.neubiorev.2019.05.023.

16. Wang J, Korczykowski M, Rao H, Fan Y, Pluta J, Gur RC, McEwen BS et al., Gender Difference in Neural Response to Psychological Stress. Soc Cogn Affect Neurosci. 2(3): 227-239, 2007, https://doi.org/10.1093/scan/nsm018

17. Pruessner JC, Dedovic K, Khalili-Mahani N, Dagher A, Meaney MJ, Lupien S, et al., Deactivation of the Limbic System During Acute Psychosocial Stress: Evidence From Positron Emission Tomography and Functional Magnetic Resonance Imaging Studies. Biol Psychiatry. 63(2): 234-40, 2008, https://doi.org/10.1016/j.biopsych.2007.04.041.

18. Sarlo GL, Holton KF, Brain Concentrations of Glutamate and GABA in Human Epilepsy: A Review. Seizure. 91: 213-227, 2021, https://doi.org/10.1016/j.seizure.2021.06.028

19. Sieghart W, Savić MM, International Union of Basic and Clinical Pharmacology. cvi: $GABA_A$ Receptor Subtype- and Function-Selective Ligands: Key Issues in Translation to Humans. Pharmacological Reviews. 70(4): 836-878, 2018, https://doi.org/10.1124/pr.117.014449

20. Bettler B, Kaupmann K, Mosbacher J, Gassmann M, Molecular Structure and Physiological Functions of $GABA_B$ receptors. Physiological Reviews. 84(3), 835-867, 2004, https://doi.org/10.1152/physrev.00036.2003

21. Chebib M, Johnston GAR, The 'ABC' of GABA receptors: A Brief Review. Clinical and Experimental Pharmacology and Physiology. 26(11): 937-940, 1999, https://doi.org/10.1046/j.1440-1681.1999.03151.x

22. Perucca E, Bialer M, White HS, New GABA-Targeting Therapies for the Treatment of Seizures and Epilepsy: I. Role of GABA as a Modulator of Seizure Activity and Recently Approved Medications Acting on the GABA System. CNS Drugs. 37(9): 755-779, 2023, https://doi.org/10.1007/s40263-023-01027-2

23. Bowery NG, International Union of Pharmacology. XXXIII. Mammalian Gamma - Aminobutyric Acid B receptors: Structure and Function. Pharmacological Reviews. 54(2): 247-264, 2002, https://doi.org/10.1124/pr.54.2.247

24. Han HA, Cortez MA, Snead OC III., $GABA_B$ Receptor and Absence Epilepsy. Jasper's Basic Mechanisms of the Epilepsies. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012, https://www.ncbi.nlm.nih.gov/books/NBK98192/

25. Ni RJ, Huang ZH, Shu YM, Wang Y, Li T, Zhou JN, Atlas of the Striatum and Globus Pallidus in the Tree Shrew: Comparison with Rat and Mouse. Neurosci Bull. 34(3): 405-418, 2018, https://doi.org/10.1007/s12264-018-0212-z

26. Iadarola MJ, Gale K. Substantia Nigra: Site of Anticonvulsant Activity Mediated by γ-Aminobutyric Acid. Science. 218(4578), 1237-1240, 1982, https://doi.org/10.1126/science.7146907

27. Young CB, Reddy V, Sonne J. Neuroanatomy, Basal Ganglia. Island (FL): StatPearls Publishing, Updated 2022, https://www.ncbi.nlm.nih.gov/books/NBK537141/

28. Lanciego JL, Luquin N, Obeso JA. Functional Neuroanatomy of the Basal Ganglia. Cold Spring Harb Perspect Med. 2(12): a009621, 2012, https://doi.org/10.1101/cshperspect.a009621

29. Basal Ganglia. (n.d.), Cleveland Clinic. https://my.clevelandclinic.org/health/body/23962-basal-ganglia

30. Albin RL, Mink JW, Recent Advances in Tourette Syndrome Research. Trends Neurosci. 29(3): 175-82, 2006, https://doi.org/10.1016/j.tins.2006.01.001.

31. Worbe Y, Baup N, Grabli D, Chaigneau M, Mounayar S, MacCairn K, et al., Behavioral and Movement Disorders Induced by Local Inhibitory Dysfunction in Primate Striatum. Cerebral Cortex. 19(8), 1844–1856, 2009, https://doi.org/10.1093/cercor/bhn214

32. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma J Jr, et al., D1 and D2 Dopamine Receptor-Regulated Gene Expression of Striatonigral and Striatopallidal Neurons. Science. 250(4986):1429-32 1990, https://doi.org/10.1126/science.2147780.

33. Kravitz AV, Freeze BS, Parker PRL, Kay K, Thwin MT, Deisseroth K, et al., Regulation of Parkinsonian Motor Behaviours by Optogenetic Control of Basal Ganglia Circuitry. Nature. 466(7306): 622-6, 2010, https://doi.org/10.1038/nature09159.

34. Rommelfanger K, Wichmann T, Extrastriatal Dopaminergic Circuits of the Basal Ganglia. Frontiers in Neuroanatomy, 4, 2010, https://doi.org/10.3389/fnana.2010.00139

35. Crossman AR, Primate Models of Dyskinesia: the Experimental Approach to the Study of Basal Ganglia-Related Involuntary Movement Disorders. Neuroscience. 21(1):1-40. PMID: 2955248, 1987, https://doi.org/10.1016/0306-4522(87)90322-8.

36. Obeso JA, Rodriguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, et al., Functional Organization of the Basal Ganglia: Therapeutic Implications for Parkinson's Disease. Mov Disord. 23(Suppl 3): S548-559, 2008, https://doi.org/10.1002/mds.22062.

37. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Artieda J, Gonzalo N, Olanow CW, et al., Pathophysiology of the Basal Ganglia in Parkinson's Disease. Trends Neurosci. 23(Suppl10): S8-19, 2000, https://doi.org/10.1016/s1471-1931(00)00028-8.

38. Lorenz RC, Gleich T, Buchert R, Schlagenhauf F, Kühn S, Gallinat J, Interactions Between Glutamate, Dopamine, and the Neuronal Signature of Response Inhibition in the Human Striatum. Hum Brain Mapp. 36(10): 4031-40, 2015, https://doi.org/10.1002/hbm.22895.

39. Nambu A. A New Dynamic Model of the Cortico-Basal Ganglia Loop. Prog Brain Res. 143: 461-6, 2004, https://doi.org/10.1016/S0079-6123(03)43043-4.

40. Nambu A. A New Approach to Understand the Pathophysiology of Parkinson's Disease. J Neurol. 252 (Suppl 4): IV1-IV4., 2005, https://doi.org/10.1007/s00415-005-4002-y.

41. Nambu A, Tokuno H, Takada M, Functional Significance of the Cortico-Subthalamo-Pallidal 'Hyperdirect' Pathway. Neurosci Res. 43(2):111-7, 2002, https://doi.org/10.1016/s0168-0102(02)00027-5.

42. Nambu A, Takada M, Inase M, Tokuno H, Dual Somatotopical Representations in the Primate Subthalamic Nucleus: Evidence for Ordered but Reversed Body-Map Transformations From the Primary Motor Cortex and the Supplementary Motor Area. J Neurosci. 16(8): 2671-83, 1996, https://doi.org/10.1523/JNEUROSCI.16-08-02671.1996.

43. Mouroux M, Hassani OK, Féger J. Electrophysiological Study of the Excitatory Parafascicular Projection to the Subthalamic Nucleus and Evidence for Ipsi- and Contralateral Controls. Neuroscience. 67(2): 399-407, 1995, https://doi.org/10.1016/0306-4522(95)00032-e.

44. Crossman AR, Mitchell IJ, Sambrook MA, Jackson A, Chorea and Myoclonus in the Monkey Induced by Gamma-Aminobutyric Acid Antagonism in the Lentiform Complex: The Site of Drug Action and a Hypothesis for the Neural Mechanisms of Chorea. Brain. (Pt 5):1211-33,1988, https://doi.org10.1093/brain/111.5.1211.

45. Graybiel AM, Ragsdale CW Jr, Yoneoka ES, Elde RP, An Immunohistochemical Study of Enkephalins and Other Neuropeptides in the Striatum of the Cat with Evidence that the Opiate Peptides are Arranged to Form Mosaic Patterns in Register with the Striosomal Compartments Visible by Acetylcholinesterase Staining. Neuroscience. 6(3): 377-97, 1981, https://doi.org/10.1016/0306-4522(81)90131-7.

46. Gerfen CR. The Neostriatal Mosaic: Compartmentalization of Corticostriatal Input and Striatonigral Output Systems. Nature. 311(5985): 461-4, 1984, https://doi.org/10.1038/311461a0.

47. Mériaux C, Franck J, Park DB, Quanico J, Kim YH, Chung CK, et al., Human Temporal Lobe Epilepsy Analyses By Tissue Proteomics. Hippocampus. 24: 628-642, 2014, https://doi.org/10.1002/hipo.22246

48. Schwartz J, Begley S, The Mind and the Brain: Neuroplasticity and the Power of Mental Force. Harper Perennial, 2003, The mind and the brain: Neuroplasticity and the power of mental force. (apa.org)

49. Mahone ME, Puts NA, Edden RAE, Ryan M, Singer HS, GABA and Glutamate in Children with Tourette Syndrome: A 1H MR Spectroscopy Study at 7T. Psychiatry Research: Neuroimaging. 273: 46-53, 2018, https://doi.org/10.1016/j.pscychresns.2017.12.005.

50. McCairn KW, Bronfeld M, Belelovsky K, Bar-Gad I, The Neurophysiological Correlates of Motor Tics Following Focal Striatal Disinhibition. Brain. 132(Pt 8): 2125-38, 2009, https://doi.org/10.1093/brain/awp142.

51. Szelies B, Weber-Luxenburger G, Pawlik G, Kessler J, Holtoff V, Mielke R, et al., MRI-Guided Flumazenil- and FDG-PET in Temporal Lobe Epilepsy. Neuroimage. 3(2): 109-18, 1996, https://doi.org/10.1006/nimg.1996.0013.

52. François C, Grabli D, McCairn K, Jan C, Karachi C, Hirsch EC, et al., Behavioural Disorders Induced by External Globus Pallidus Dysfunction in Primates II. Anatomical Study. Brain. 127(Pt 9): 2055-70, 2004, https://doi.org/10.1093/brain/awh239.

53. Karachi C, Grabli D, Baup N, Mounayar S, Tandé' D, François C, et al., Dysfunction of the Subthalamic Nucleus Induces Behavioral and Movement Disorders in Monkeys. Mov Disord. 24(8): 1183-92, 2009, https://doi.org/10.1002/mds.22547.

54. Augustine F, Singer HS. Merging the Pathophysiology and Pharmacotherapy of Tics. Tremor Other Hyperkinet Mov (N Y). 8: 595, 2019, https://doi.org/10.7916/D8H14JTX.

55. Wu C, Sun D, GABA Receptors in Brain Development, Function, and Injury. Metab Brain Dis. 30(2): 367-79, 2015, https://doi.org/10.1007/s11011-014-9560-1.

56. Crossman AR, Sambrook MA, Jackson A, Experimental Hemichorea/Hemiballismus in the Monkey. Studies on the Intracerebral Site of Action in a Drug-Induced Dyskinesia. Brain. 107(2): 579-96, 1984, https://doi.org/10.1093/brain/107.2.579.

57. Stern E, Silversweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, et al., A Functional Neuroanatomy of Tics in Tourette Syndrome. Arch Gen Psychiatry. 57(8): 741-8, 2000, https://doi.org/10.1001/archpsyc.57.8.741.

58. Lerner A, Bagic A, Boudreau EA, Hanakawa T, Pagan F, Mari Z, et al., Neuroimaging of Neuronal Circuits Involved in Tic Generation in Patients with Tourette Syndrome. Neurology. 68(23):1979-87, 2007, https://doi.org/10.1212/01.wnl.0000264417.18604.12.

59. Inase M, Tokuno H, Nambu A, Akazawa T, Takada M, Corticostriatal and Corticosubthalamic Input Zones from the Presupplementary Motor Area in the Macaque Monkey: Comparison with the Input Zones from the Supplementary Motor Area. Brain Res. 833(2):191-201, 1999, https://doi.org/10.1016/s0006-8993(99)01531-0.

60. Takada M, Tokuno H, Nambu A, Inase M. Corticostriatal Projections from the Somatic Motor Areas of the Frontal Cortex in the Macaque Monkey: Segregation Versus Overlap of Input Zones from the Primary Motor Cortex, the Supplementary Motor Area, and the Premotor Cortex. Exp Brain Res. 120(1):114-28, 1998, https://doi/10.1007/s002210050384.

61. Takada M, Tokuno H, Nambu A, Inase M. Corticostriatal Input Zones From the Supplementary Motor Area Overlap Those From the Contra- Rather Than Ipsilateral Primary Motor Cortex. Brain Res. 791(1-2): 335-40, 1998, https://doi.org/10.1016/s0006-8993(98)00198-x.

62. Cavada C, Goldman-Rakic PS, Topographic Segregation of Corticostriatal Projections From Posterior Parietal Subdivisions in the Macaque Monkey. Neuroscience 42(3): 683-96, 1991, https://doi.org/10.1016/0306-4522(91)90037-o.

63. Yeterian EH, Pandya DN, Prefrontostriatal Connections in Relation to Cortical Architectonic Organization in Rhesus Monkeys. J Comp Neurol. 312(1):43-67, 1991, https://doi.org/10.1002/cne.903120105.

64. Gerardin E, Pochon JB, Poline JB, Tremblay L, Van de Moortele PF, Levy R, et al., Distinct Striatal Regions Support Movement Selection, Preparation and Execution. Neuroreport. 15(15): 2327-31, 2004, https://doi.org/10.1097/00001756-200410250-00005.

65. Bohlhalter S, Goldfine A, Matteson S, Garraux G, Hanakawa T, Kansaku K, et al., Neural Correlates of Tic Generation in Tourette Syndrome: An Event-Related Functional MRI Study. Brain. 129(Pt 8): 2029-37, 2006, https://doi.org/10.1093/brain/awl050.

66. Turrigiano G. Homeostatic Synaptic Plasticity: Local and Global Mechanisms For Stabilizing Neuronal Function. Cold Spring Harb Perspect Biol. 4(1): a005736, 2012, https://doi.org/10.1101/cshperspect.a005736.

67. Turrigiano GG, Nelson SB. Homeostatic Plasticity in the Developing Nervous System. Nat Rev Neurosci. 5(2): 97-107, 2004, https://doi.org/10.1038/nrn1327.

68. Paradis S, Sweeney ST, Davis GW, Homeostatic Control of Presynaptic Release is Triggered by Postsynaptic Membrane Depolarization. Neuron. 30(3): 737-49, 2001, https://doi.org/10.1016/s0896-6273(01)00326-9.

69. Sperk G, Furtinger S, Schwarzer C, Pirker S, (2004). GABA and its Receptors in Epilepsy. In GABA and its receptors in epilepsy. Springer US., 2004 https://doi.org/10.1007/978-1-4757-6376-8_7

70. Vertkin I, Styr B, Slomowitz E, Ofir N, Shapira I, Berner D, et al., GABAB Receptor Deficiency Causes Failure of Neuronal Homeostasis in Hippocampal Networks. Proc Natl Acad Sci U S A.112(25): E3291-9, 2015, https://doi.org/10.1073/pnas.1424810112.

71. Straessle A, Loup F, Arabadzisz D, Ohning GV, Fritschy JM, Rapid and Long-Term Alterations of Hippocampal GABAB Receptors in a Mouse Model of Temporal Lobe Epilepsy. Eur J Neurosci. 18(8): 2213-26, 2003, https://doi.org/10.1046/j.1460-9568.2003.02964.x.

72. Sloviter RS, Permanently Altered Hippocampal Structure, Excitability, and Inhibition After Experimental Status Epilepticus in the Rat: The "Dormant Basket Cell" Hypothesis and Its Possible Relevance to Temporal Lobe Epilepsy. Hippocampus. 1(1): 41-66, 1991, https://doi.org/10.1002/hipo.450010106.

73. Brodie MJ, Besag F, Ettinger AB, Mula M, Gobbi G, Comai S, et al., Epilepsy, Antiepileptic Drugs, and Aggression: An Evidence-Based Review. Pharmacol Rev. 68(3): 563-602, 2016, https://doi.org/10.1124/pr.115.012021.

74. Dubanet O, Ferreira Gomes Da Silva A, Frick A, Hirase H, Beyeler A, Leinekugel X, Probing the Polarity of Spontaneous Perisomatic GABAergic Synaptic Transmission in the Mouse CA3 Circuit in Vivo. Cell Reports. 36(2): 109381, 2021, https://doi.org/10.1016/j.celrep.2021.109381

75. Huberfeld G, Wittner L, Clemenceau S, Baulac M, Kaila K, Miles R, Rivera C. Perturbed Chloride Homeostasis and GABAergic Signaling in Human Temporal Lobe Epilepsy. J Neurosci. 27(37): 9866-73, 2007, https://doi.org/10.1523/JNEUROSCI.2761-07.2007.

76. Kourdougli N, Pellegrino C, Renko JM, Khirug S, Chazal G, Kukko-Lukjanov TK, et al., Depolarizing γ-Aminobutyric Acid Contributes to Glutamatergic Network Rewiring in Epilepsy. Ann Neurol. 81(2): 251-265, 2017, https://doi.org/10.1002/ana.24870.

77. Chavas J, Marty A. Coexistence of Excitatory and Inhibitory GABA Synapses in the Cerebellar Interneuron Network. J Neurosci. 23(6): 2019-31, 2003, https://doi.org/10.1523/JNEUROSCI.23-06-02019.2003.

78. Hansen CC, Ljung H, Brodtkorb E, Reimers A, Mechanisms Underlying Aggressive Behavior Induced by Antiepileptic Drugs: Focus on Topiramate, Levetiracetam, and Perampanel. Behav Neurol. 2018: 2064027, 2018, https://doi.org/10.1155/2018/2064027.

79. Czuczwar SJ. Układ GABA-ergiczny a Leki Przeciwpadaczkowe, GABA-ergic System and Antiepileptic Drugs. Neurol Neurochir Pol. 34(Suppl 1):13-20, Polish, 2000, https://pubmed.ncbi.nlm.nih.gov/10768141/

80. Perucca E, White HS, Bialer M, New GABA-Targeting Therapies for the Treatment of Seizures and Epilepsy: II. Treatments in Clinical Development. CNS Drugs. 37(9): 781-795. 2023, https://doi.org/10.1007/s40263-023-01025-4

81. Rogeau A, Nordio G, Veronese M, Brown K, Nour MN, Osugo M, et al.,The Relationship Between Glutamate, Dopamine, and Cortical Gray Matter: A Simultaneous PET-MR Study. Mol Psychiatry. 27(8): 3493-3500, 2022, https://doi.org/10.1038/s41380-022-01596-6.

82. Burman RJ, Rosch RE, Wilmshurst JM, Sen A, Ramantani G, Akerman CJ, et al., Why Won't It Stop? The Dynamics of Benzodiazepine Resistance in Status Epilepticus. Nature Reviews Neurology. 18(7): 428-441, 2022, https://doi.org/10.1038/s41582-022-00664-3

83. Kienitz R, Kay L, Beuchat I, Gelhard S, von Brauchitsch S, Mann C, et al., Benzodiazepines in the Management of Seizures and Status Epilepticus: A Review of Routes of Delivery, Pharmacokinetics, Efficacy, and Tolerability. CNS Drugs. 36(9): 951-975, 2022, https://doi.org/10.1007/s40263-022-00940-2

84. Janković SM, Dješević M, Janković SV, Experimental GABA A Receptor Agonists and Allosteric Modulators for the Treatment of Focal Epilepsy. Journal of Experimental Pharmacology.13: 235-244, 2021, https://doi.org/10.2147/jep.s242964

85. Fritschy JM, Kiener T, Bouilleret V, Loup F, GABAergic Neurons and GABAA-Receptors in Temporal Lobe Epilepsy. Neurochemistry International, 34(5): 435-445, 1999, https://doi.org/10.1016/s0197-0186(99)00040-6

86. Reddy DS, Carver CM, Clossen B, Wu X, Extrasynaptic γ-Aminobutyric Acid Type A Receptor–Mediated Sex Differences in the Antiseizure Activity of Neurosteroids in Status Epilepticus and Complex Partial Seizures. Epilepsia, 60(4): 730-743, 2019, https://doi.org/10.1111/epi.14693

87. Fariba KA, Saadabadi A, Topiramate. StatPearls, Treasure Island (FL), 2023, https://www.ncbi.nlm.nih.gov/books/NBK554530/

88. Rahman M, Awosika AO, Nguyen H, Valproic Acid. StatPearls, Treasure Island (FL), 2023, https://www.ncbi.nlm.nih.gov/books/NBK559112/

89. Owen RM, Blakemore D, Cao L, Flanagan N, Fish R, Gibson KR, et al., Design and Identification of a Novel, Functionally Subtype Selective GABAA positive allosteric modulator (PF-06372865). Journal of Medicinal Chemistry. 62(12): 5773-5796, 2019, https://doi.org/10.1021/acs.jmedchem.9b00322

90. Food and Drug Administration, Doc. No. 4955025, 2022, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215904s000lbl.pdf

91. FDA approves new treatment for adults with partial-onset seizures [Press release], 2019, https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-partial-onset-seizures

92 Ontozry (Cenobamate). European Union European Medicines Agency, 2021, https://www.ema.europa.eu/en/medicines/human/EPAR/ontozry

93. Sharma R, Positive Allosteric Modulation of GABAA Receptors by a Novel Antiepileptic Drug Cenobamate. European Journal of Pharmacology, 879: 173117, 2020, https://doi.org/10.1016/j.ejphar.2020.173117

94. Engrail Therapeutics INC., ENACT: A Study of ENX-101 as Adjunctive Treatment in Patients With Focal Seizures (ENACT). Identifier NCT05481905., 2022, Study Details | ENACT: A Study of ENX-101 as Adjunctive Treatment in Patients With Focal Seizures | ClinicalTrials.gov

95. Engrail Therapeutics Announces Positive Results of ENX-101 Phase 1b Clinical Study and Prepares for Initiation of ENACT Phase 2 Trial in Focal Epilepsy, 2022, https://www.businesswire.com/news/home/20220607005544/en/Engrail-Therapeutics-Announces-Positive-Results-of-ENX-101-Phase-1b-Clinical-Study-and-Prepares-for-Initiation-of-ENACT-Phase-2-Trial-in-Focal-Epilepsy

96. Sarkar J, Wakefield S, MacKenzie G, Moss SJ, Maguire J, Neurosteroidogenesis is Required for the Physiological Response to Stress: Role of Neurosteroid-Sensitive GABAA Receptors. J Neurosci. 31(50): 18198-210, 2011, https://doi.org/10.1523/JNEUROSCI.2560-11.2011.

97. Bowers G, Cullinan WE, Herman JP, Region-Specific Regulation of Glutamic Acid Decarboxylase (GAD) mRNA Expression in Central Stress Circuits. J Neurosci.1;18(15): 5938-47, 1998, https://doi.org/10.1523/JNEUROSCI.18-15-05938.1998.

98. Mody I, Maguire J, The Reciprocal Regulation of Stress Hormones and GABA(A) Receptors. Front Cell Neurosci. 6:4, 2012, https://doi.org/10.3389/fncel.2012.00004.

99. Di Cristo G, Awad PN, Hamidi S, Avoli M. KCC2, Epileptiform Synchronization, and Epileptic Disorders. Prog Neurobiol.162: 1-16, 2018, https://doi.org/10.1016/j.pneurobio.2017.11.002.

100. Cano-López I, González-Bono E, Cortisol Levels and Seizures in Adults with Epilepsy: A Systematic Review. Neurosci Biobehav 103: 216-229, 2019, https://doi.org/10.1016/j.neubiorev.2019.05.023.

101. Acosta GB, Otero Losada ME, Rubio MC, Area-Dependent Changes in GABAergic Function After Acute and Chronic Cold Stress. Neurosci Lett. 154(1-2):175-8, 1993, https://10.1016/0304-3940(93)90200-5.

102. Joshi K, Cortez MA, Snead OC, Targeting the GABAB Receptor for the Treatment of Epilepsy. Springer International, 2016, https://doi.org/10.1007/978-3-319-46044-4_10

103. Khosravani H, Zamponi GW, Voltage-Gated Calcium Channels and Idiopathic Generalized Epilepsies. Physiological Reviews, 86(3): 941-966, 2006, https://doi.org/10.1152/physrev.00002.2006

104. de la Peña E, Geijo-Barrientos E, Laminar Localization, Morphology, and Physiological Properties of Pyramidal Neurons that Have the Low-Threshold Calcium Current in the Guinea-Pig Medial Frontal Cortex. The Journal of Neuroscience, 16(17): 5301-5311, 1996, https://doi.org/10.1523/jneurosci.16-17-05301.1996

105. Drugs.com, Baclofen. (n.d.), https://www.drugs.com/baclofen.html

106. Drugs.com. Baclofen side effects. (n.d.)., https://www.drugs.com/sfx/baclofen-side-effects.html

107. NRTX-1001: Human Inhibitory Neuron Cell Therapy Suppresses Seizures and Reduces Histopathology in Mouse Model of Chronic Epilepsy With High Repeatability Across Multiple Studies and Manufacturing Lots (Abstract No. 1.277) American Epilepsy Society (n.d.). https://aesnet.org/abstractslisting/nrtx-1001--human-inhibitory-neuron-cell-therapy-suppresses-

seizures-and-reduces-histopathology-in-mouse-model-of-chronic-epilepsy-with-high-repeatability-across-multiple-studies-and-manufacturing-lots

108. Neurona Therapeutics, FIH Study of NRTX-1001 Neural Cell Therapy in Drug-Resistant Unilateral Mesial Temporal Lobe Epilepsy. Identifier NCT05135091., 2022, Study Details | FIH Study of NRTX-1001 Neural Cell Therapy in Drug-Resistant Unilateral Mesial Temporal Lobe Epilepsy | ClinicalTrials.gov

109. Neurona Theraputics, Neurona Therapeutics Announces Initial Subject Dosed in First Clinical Trial of Regenerative Human Cell Therapy, NRTX-1001, in Adults With Drug-Resistant Focal Epilepsy [Press release], 2022, https://www.neuronatherapeutics.com/news/press-releases/062922/

110. Neurona Theraputics. (2022, December 5). Neurona Therapeutics presents clinical data for NRTX-1001 regenerative cell therapy for drug-resistant focal epilepsy at American Epilepsy Society annual meeting [Press release]. https://www.globenewswire.com/news-release/2022/12/05/2567333/0/en/Neurona-Therapeutics-Presents-Clinical-Data-for-NRTX-1001-Regenerative-Cell-Therapy-for-Drug-Resistant-Focal-Epilepsy-at-American-Epilepsy-Society-Annual-Meeting.html

111. Health, N. I. O. M., Scientists Unveil Detailed Cell Maps of the Human Brain and the Nonhuman Primate Brain [Press release], 2023, https://www.nimh.nih.gov/news/science-news/2023/scientists-unveil-detailed-cell-maps-of-the-human-brain-and-the-nonhuman-primate-brain#:~:text=%E2%80%9CThese%20new%20detailed%20cell%20atlases%20of%20the%20human,brain%20cells%20and%20circuits%20involved%20in%20brain%20disorders.%E2%80%9D