



Review

Neuroconnectivity and valproic acid: The myelin hypothesis

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ABSTRACT

Neuropsychiatric medications that directly alter the epigenome, such as valproic acid, can under certain conditions reactivate critical developmental periods and thus impact adult neuroconnectivity. In animal models valproic acid was shown to inhibit the process of postnatal myelination and to replicate age-dependent decline in remyelination efficiency. The human central nervous system's myelination process, unlike that of non-human primates commonly used in the experimental models, is an intricate heterochronous process that continues well into adult life and which probably underlies later life neurocognitive changes and plasticity. Chronic exposure to valproic acid, especially in patients with epilepsy and neuropsychiatric disorders, may profoundly affect this process and its developmental trajectory. Further studies using novel MRI methods that allow in vivo mapping of myelination trajectories across the lifespan are urgently required to address the potential effects of valproic acid on brain development.

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Contents

1. Introduction: epigenetic modulation of myelination and the role for histone deacetylase (HDAC) inhibitors	1848
2. Spatiotemporal myelination of the human brain and possible implication for cognition	1850
3. Neuropsychiatric disorders and brain myelination	1850
4. VPA's Midas touch: a direct inhibitor of HDACs with a potent antiepileptic, mood stabilizer, and putative neuroprotector effects	1852
5. Myelination, VPA and brain plasticity	1852
5.1. Epigenetic control of the oligodendrocyte identity	1852
5.2. Autism and valproic acid	1853
5.3. Critical periods for brain plasticity	1853
5.4. "Chicken and egg" problem: some as yet unanswered questions in the story of VPA and juvenile myoclonic epilepsy?	1853
6. Conclusion and future directions	1855
Conflicts of interest	1855
References	1855

1. Introduction: epigenetic modulation of myelination and the role for histone deacetylase (HDAC) inhibitors

The 21st century brought about seminal insights into the pivotal epigenetic mechanisms necessary for the establishment of cell identity and tissue formation, as well as dynamic intracellular processes for translating environmental stimuli into modifications

in gene expression (Chuang et al., 2009). Epigenetic modifications including acetylation and deacetylation of histone proteins associated with chromatin are now understood to present an integral part of an entire host of brain functions, ranging from the development of the nervous system and its basic neuronal functions to multimodal cognitive processes (Gräff et al., 2011). In addition, a substantial body of data has emerged pointing to a probable causal relationship between aberrant epigenetic modifications and a wide range of neurodevelopmental, neurodegenerative, and neuropsychiatric disorders (Gräff et al., 2011; Bartzokis, 2011). Chromatin remodeling through increased histone acetylation, and hence gene transcription, is linked with recovery of learning

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2. Spatiotemporal myelination of the human brain and possible implication for cognition

Early brain developmental processes such as neurogenesis, synaptic pruning and cell shrinkage occur primarily during the intrauterine period, and/or after birth. These reductionist processes that are commonly completed by puberty or adolescence are thought to affect several childhood disorders (Huttenlocher and Dabholkar, 1997; Rakic, 2002; Bartzokis, 2005). It has been previously argued that the regressive or pruning processes occur in order to provide the required volume, space and possibly other resources necessary to support the crucial process of myelination (Bartzokis et al., 2001; Bartzokis, 2004, 2005, 2011). In humans, the regressive processes occur in a heterochronous pattern occurring in primary unimodal process areas (motor, sensory) before multimodal association areas (frontal, temporal, and parietal lobes) (Huttenlocher and Dabholkar, 1997). Petanjek et al. (2011) recently showed that human developmental remodeling, including substantial elimination of synaptic spines, continues in the prefrontal cortex beyond adolescence and throughout the third decade of life before stabilizing at the adult level. In nonhuman primates, on the other hand, these processes occur simultaneously in all cortical regions (Rakic, 2002). At the turn of the last century, Fleschsig hypothesized that white matter (WM) tract changes provide the basis for later life brain development and improved cognitive efficiency (Flechsig, 1901). In his seminal study, Fleschsig proposed a spatiotemporal discourse and showed that myelination of the human brain continues well into middle age. Of late, a few unrelated lines of investigations converged in support of this early paradigm and a seminal insight into the time of peak of human cerebral maturation was realized (Bartzokis et al., 2004; Gao et al., 2009; Salthouse, 2009; Deoni et al., 2011; Kochunov et al., 2012).

Cognitive improvements in reasoning, spatial visualization and speed of processing continue well into the 3rd and 4th decades of life, after which point cognitive processing shows a rapid age-related decline (Salthouse, 2009). Neurocognitive changes have been associated with the lifetime changes in the integrity of associative WM (Bartzokis, 2004; Bartzokis et al., 2003, 2004; Konrad et al., 2009; Vernooij et al., 2009). In particular, fractional anisotropy (FA) values assessed by diffusion tensor imaging (DTI) in associative WM areas were correlated with performance on the neuropsychological tests sensitive to processing speed (Bartzokis et al., 2004; Konrad et al., 2009). DTI assessed FA describes the directional selectivity of the random diffusion of water molecules and higher FA values are observed along heavily myelinated WM tracts (Kochunov et al., 2012). Absolute FA values are sensitive to many parameters. Changes in regional FA values during normal maturation and aging are however thought to be predominantly due to changes in myelination and can therefore be used as indirect measurement of myelin level (Kochunov et al., 2012). Of note, another novel neuroimaging technique called mcDESPOT (multicomponent driven equilibrium single pulse observation of T1 and T2) was used recently to provide quantitative visualization of brain myelination in vivo in healthy human infancy (Fig. 2; Deoni et al., 2011). This technique is shown to correlate strongly with histological estimates of myelin content, and appears to be an even more apt marker of myelin content compared with FA (as reviewed in Deoni et al., 2011).

In a recent study, the white matter integrity was systematically assessed across the lifespan using DTI in a large cohort of 831 healthy individuals, covering over 8 decades of human life span (ages 11–90) (Kochunov et al., 2012). The changes in FA of water diffusion for eleven major cerebral WM tracts were mapped and it was shown that FA measurements for all but one major cortical WM tract (namely CST) reached peaks between 23 and 39 years of age. The maturation rates, prior to age-of-peak were significantly

correlated with the rates of decline, past age-of-peak. Regional analysis of the corpus callosum (CC) showed that thinly myelinated, densely packed fibers in the genu, that connect prefrontal areas, matured later and showed higher decline in aging than the more thickly myelinated motor and sensory areas in the body and splenium of the CC. Overall the study showed that associative, cerebral WM tracts that reach their peak FA values later in life also show progressively higher age-related decline than earlier maturing motor and sensory tracts. Furthermore, the age-range where FA values reached their maximum concurred with the age range during which the performance on various cognitive measurements was previously shown to peak (Salthouse, 2009). Interestingly, the linear rates of cerebral maturation were higher for men than women, although this difference did not reach significance. Equally, male subjects showed a significantly higher rate of FA decline. In past the neuroprotective properties of estrogen and environmental interactions have all been proposed as putative mechanisms behind the observed gender differences (Kochunov et al., 2012). The reduction in density of glial cells and an apparent reduction in myelin levels were shown to be associated with the decline in FA with age (Kochunov et al., 2010). It was suggested that changes in essential neurocognitive functions such as processing speed and executive function across the lifespan were related to changes in the integrity of thinly myelinated multimodal associative areas, likely reflecting the changes in the propagation of speed of action potentials across cortical networks (Bartzokis et al., 2004; Bartzokis, 2011; Kochunov et al., 2010, 2012). Taken together these findings beget important inferences for the clinical studies of neuropsychiatric disorders.

3. Neuropsychiatric disorders and brain myelination

The oligodendrocytes are the glial cell type most consistently implicated in mood disorders (Price and Drevets, 2010). It is likely that reduction in oligodendrocytes may arise secondary to an effect on myelin, either through demyelination, abnormal development, or atrophy in the number of myelinated axons. Myelin staining was reported to be decreased in the deep WM of the dorsolateral prefrontal cortex in major depressive disorder (MDD) and bipolar affective disorder (BD) subjects; whereas the WM volumes of the genu and splenial portions of the corpus callosum were abnormally reduced in MDD and BD (Price and Drevets, 2010). Moreover, the deficits in glia in the cerebral cortex were reported to be the greatest in layers III, V, and VI (Vostrikov et al., 2007; Price and Drevets, 2010). Since these layers contain the intracortical plexuses of myelinated fibers (bands of Baillarger, layers III and V), or a large component of myelinated fibers running between the gray and white matter (e.g. layer VI) this further supports the supposition that myelinating oligodendrocyte function is reduced in MDD (Price and Drevets, 2010).

In a continually dividing and differentiating cell line such as oligodendrocytes, epigenetic modifications of gene expression can be introduced in each subsequent generation of differentiating cells and thus reflect environmental conditions at different stages of the lifespan (Bartzokis, 2011). This susceptibility of the myelination process to genetic and environmental insults likely underlies our brain's unique vulnerability to developmental disorders such as autism, learning disabilities, attention-deficit/hyperactivity disorder, schizophrenia (SZ), BD and addiction (Bartzokis, 2004, 2005; Ha et al., 2011). Equally, it has been argued the shared deficits in inhibitory controls between all these disorders make the high rates of comorbid addiction an expected functional epiphenomenon (Bartzokis, 2005). Namely the quadratic relationship of the inhibitory responses was shown to be similar to the quadratic trajectory of myelination, in which peak myelination in the frontal lobe is not achieved until middle age (for review, see Bartzokis,

studies in pediatric epileptic patients where its use has been associated with varied cognitive deficits (Goldberg and Burdick, 2001). Evidence in the literature is equally sparse for its impact on cognitive symptoms in neuropsychiatric disorders, such as for example SZ, ADHD and BD, in all age groups (Schwarz et al., 2010; Washburn et al., 2011; Larrison et al., 2011).

4. VPA's Midas touch: a direct inhibitor of HDACs with a potent antiepileptic, mood stabilizer, and putative neuroprotector effects

Since its original discovery in France in early 60s as an analog of valeric acid, this wide-spectrum antiepileptic in the form of sodium valproate has become known as one of the mainstays for the treatment of different epileptic syndromes in adults and children (Perucca, 2002). It is commonly considered a first-choice drug for most forms of idiopathic and symptomatic generalized epilepsies and it has been shown to be effective in multiple seizure types, including tonic–clonic, myoclonic and absence seizures. In some countries, intravenous preparations are increasingly used in the treatment of convulsive and nonconvulsive status epilepticus (Perucca, 2002). VPA is FDA approved as a mood stabilizer for the treatment of manic episodes associated with BD; it is also used for the prophylaxis of migraine headaches and post traumatic epilepsy (Henry, 2003; D'Ambrosio and Perucca, 2004; Rosenberg, 2007; Nalivaeva et al., 2009). It is relatively free of side-effects compared to other antiepileptics and is routinely used in epileptic patients, such as in those with juvenile myoclonic epilepsy (JME), in some cases successfully for decades (as reviewed in Perucca, 2002; Henry, 2003). Despite its long-standing usage, its multi-faceted mechanism of action is still matter of some scientific controversy.

As reviewed by Perucca (2002), there is by now substantial evidence that VPA increases γ -aminobutyric acid (GABA) synthesis and release and hence potentiates GABAergic transmission in specific brain regions. It also releases the excitatory amino acid β -hydroxybutyric acid and attenuates neuronal excitation mediated by activation of N-methyl-D-aspartate (NMDA) glutamate receptors. Its direct action on excitable membranes was also reported, including blockade of voltage-dependent sodium channels. Additionally, VPA modulates dopaminergic and serotonergic transmission (Perucca, 2002). These putative mechanisms are speculated to be behind its efficacy in a number of in vitro and animal models of neurological and neuropsychiatric disorders such as SZ, stroke, motor neuron disease, Alzheimer's and Huntington's disease, where its use has been recently progressively investigated (Nalivaeva et al., 2009). Moreover, VPA in addition to highly active antiretroviral therapy showed a reduction in latent HIV infection, suggesting a potential role in the treatment of this illness as well (Lehrman et al., 2005). Furthermore, the role for VPA in the treatment of systematic lupus erythematosus, various cancers, and other therapeutic potential ranging from anti-infective agents to treatments for hemoglobinopathies is currently being investigated (as reviewed in Nalivaeva et al., 2009). VPA treatment produces marked alterations in the expression of multiple genes, many of which are involved in transcription regulation, cell survival, ion homeostasis, cytoskeletal modifications and signal transduction (Rosenberg, 2007). It is now by and large reasoned that its action as a pan-inhibitor of HDACs is also underlying the majority of the above listed, speculated neuroprotective and anti-cancer actions (Nalivaeva et al., 2009).

Class I (HDACs 1–3, 8) and Class IIa (HDACs 4, 5, 7, 9) isoforms appear to be strongly inhibited by this antiepileptic (Chuang et al., 2009). On the whole, many of Class I and Class IIa HDAC inhibitors have been shown to restore histone acetylation status and improve

neuronal plasticity in the CNS; they appear to improve learning and memory and to reverse spatial memory defects in animal models (see Fig. 2; as reviewed in Chuang et al., 2009; Nalivaeva et al., 2009; Dietz and Casaccia, 2010; Fischer et al., 2010). Notwithstanding this, VPA may through pan-inhibition also exhibit toxicity in various cell types of the CNS (Fig. 2; Chuang et al., 2009; Dietz and Casaccia, 2010; Fischer et al., 2010). Hence, for any neurological or neuropsychiatric disease it is important to take into account the effect of HDACs on all cell types in the CNS, namely neuronal, glial and inflammatory cells and to clearly define their relative contribution to the physiological/pathological process (Fig. 2; Dietz and Casaccia, 2010). It is conceivable that the opposing effects on distinct cell types profoundly influence the overall therapeutic potential of pan-HDAC inhibitors such as VPA itself. So hypothetically speaking, in distinct neurobiological milieus, VPA via its biochemical, molecular and epigenetic mechanisms may simultaneously act to promote pro-neuronal survival and proliferation while also negatively affecting differentiation of local oligodendrocyte progenitor cell pools; in a given critical window of development for that distinct microcircuitry the net precise effect could prove functionally caustic. Perhaps in line with this argument, although VPA has been proposed as a possible therapeutic option in a variety of neurodegenerative diseases, inclusive of Alzheimer's disease (Nalivaeva et al., 2009; Monti et al., 2009), recently its role in the treatment of this illness has been seriously questioned. Specifically, in group of patients with mild to moderate Alzheimer's disease the divalproex sodium formulation of VPA was associated with accelerated cognitive impairment and increased brain volume loss over 1 year (Fleisher et al., 2011). It may be, however, that selective HDAC inhibitors have greater potential in treating late-onset neurodegenerative disease since different HDACs exhibit differing neuronal actions. For example, HDAC1 inhibition is associated with neurotoxicity (Kim et al., 2008) whereas HDAC3 activity is selectively toxic to neurons (Bardai and D'Mello, 2011).

5. Myelination, VPA and brain plasticity

Continual myelination of the human brain likely endorses plasticity of neuronal networks and learning throughout life. It has been previously contended that it may increase the processing capacity of the brain's connectivity up to 3000-fold and thus progressively enable development of advanced cognitive functions (Bartzokis, 2011). For this, an uninterrupted recruitment and differentiation of later myelinating oligodendrocytes might prove a functional bottleneck (Lamantia and Rakic, 1990; Bartzokis, 2011).

5.1. Epigenetic control of the oligodendrocyte identity

The neurobiology of previously described regional heterochronicity is yet to be fully unraveled. However, microscopy studies have shown that oligodendrocytes that myelinate primary motor and sensory tracts are morphologically distinct from the later differentiating ones that myelinate the associative tracts connecting multimodal areas (Kochunov et al., 2012). The monomodal WM tracts that mainly consist of large diameter axons are myelinated by a single oligodendrocyte per myelin segment. In contrast, a single oligodendrocyte serves up to 50 axons in multimodal areas, further emphasizing the impact that any potential inhibition of this later process may cause (Lamantia and Rakic, 1990; Kochunov et al., 2012). Oligodendrocyte differentiation and maturation (Fig. 1) in various brain regions is likely orchestrated by highly interlinked and distinct genetic and epigenetic programs. The full intricacies of this process are far from clear with the majority of available data stemming from animal models (Yu et al., 2010). Histone modifications and HDACs were all suggested as vital parts of the

involved epigenetic machinery and during the last decade a variety of chemicals were reported to possess an HDAC inhibitory effect. Thus far the effects of VPA in chromatin remodeling have been met with much excitement and a number of proposed future uses has been brought forward, all based on its beneficial effects against epilepsy, malignancy and as a purported neuroprotector (Nalivaeva et al., 2009; Monti et al., 2009). Notwithstanding this, it also became manifest that therapeutical levels of VPA, via presumed inhibitory effects on Class 1 HDACs, interfere with progression of oligodendrocyte differentiation in animal models of developmental myelination and remyelination (Fig. 1; Shen et al., 2005, 2008). One could argue that any such dramatic covert effects in humans are highly unlikely given its well characterized side effects profile and wide usage for almost half a century. However, it was only recently that another, potentially related major clinical concern of VPA use, has been brought to light. More specifically, in utero exposure was associated with long term effects on infants' cognitive development (Adab et al., 2004; Meador et al., 2009). No biological mechanisms have so far been put forward as an explanation but yet another decade later and this time its use in dementia has been questioned due to reported detrimental cognitive and white matter effects (Fleisher et al., 2011). Even that caution needs to be exercised in interpreting these early results, they do however come on the heels of numerous past findings and reports about reversible cerebral atrophy and dementia associated with VPA therapy in patients, even without hyperammonemia or toxicity present. Osmotic changes, inhibition of neurofilament production/neurite outgrowth, mitochondrial toxicity and increased clearance of abnormally folded proteins were all at times postulated as possible biological triggers (Guerrini et al., 1998; Fleisher et al., 2011). Thus far the role for aberrant myelination in some of these changes has not been considered.

5.2. Autism and valproic acid

It is now recognized that prenatal exposure to VPA confers an increased risk of neural tube defects (e.g. 1–2% incidence of *spina bifida aperta*, a closure defect of the posterior neural tube) and some other minor dysmorphic features, the true incidence of which remains controversial (Shorvon, 2004; Zhang et al., 2010). Although various underlying pathomechanisms have been suggested, including the interaction of VPA with embryonic folate metabolism and HDACs-related events, the exact mechanism of action at play is still far from clear (Zhang et al., 2010). Furthermore, human embryonic exposure to VPA during a strict time window of 20–24 days post conception appears to be linked to a seven-fold increased likelihood of developing autism (LeBlanc and Fagiolini, 2011). Similarly, robust rodent VPA models of autism have been developed by injecting a single dose of VPA to a pregnant female at a time that is equivalent to the human susceptibility time window (Arndt et al., 2005; Rinaldi et al., 2008; LeBlanc and Fagiolini, 2011). In those animal models similar gross abnormalities to those in human autism have been reported inclusive of the medial prefrontal cortex, somatosensory cortex and amygdala hyperconnectivity, hyperactivity and hyperplasticity. The results were taken to suggest that increased local pyramidal cells connectivity rendered cortical microcircuits more sensitive to external stimulation so that once activated they would become more autonomous, thus impairing the ability of distal brain regions to effectively orchestrate neocortical activity in the functional modules of the neocortex. Interestingly, it was previously argued that the thick, strongly myelinated interlaminar axon collaterals of some of the fast spiking inhibitory interneurons play a pivotal role in coordinating electrical activity across the cortical minicolumn. Depending on their diameters and myelination status, the axons providing intracortical connections may

represent crucial 'delay lines' with highly tuned latencies (Thomsen and Bannister, 2003).

5.3. Critical periods for brain plasticity

In the rodent VPA models of autism, the most affected cortical areas share some common alternations. However, they also show region-specific changes which likely reflect differences in local network structures, homeostatic mechanisms strategies, in a local functional role, or in their respective developmental time courses. Interestingly, Gogolla et al. (2009) showed that prenatal exposure to VPA in mouse models induced postnatal changes similar to those observed in other mouse models modeled based on single-gene mutations previously identified in human patients (e.g. NL-3, Neuroligin, etc.). Specifically, this group highlighted the asymmetric reduction in parvalbumin (PV) positive fast spiking inhibitory interneurons in a parietal region, although other brain regions (e.g. frontal) were also significantly affected. These fast-spiking interneurons have been implicated in initiation of a critical period for cortical plasticity and in generation of gamma oscillations in the neocortex (Gogolla et al., 2009). Thus arguably their deficits, also noted in some animal models of SZ, could delay or paradoxically accelerate, critical periods in specific brain regions. Furthermore, a resultant dysregulation of oscillations could prevent discrimination of intrinsic versus extrinsic signals as well as interfere with attention, arousal, sensory processing and cognition (Gogolla et al., 2009; Vukadinovic and Rosenzweig, 2012).

It is not clear whether HDAC inhibition lies behind the observed VPA effects on the PV cells in utero, nor is it currently known what effect, if indeed any, VPA may have on those cells in later stages of neurodevelopment. Furthermore, it is possible that some observed alterations are not direct consequences of the VPA insult but the homeostatic normalization mechanisms to the primary alterations. However, given recent insights into the protracted and heterochronous nature of the developmental trajectory of the human brain circuitry, similar later-life VPA modulatory effects on brain plasticity and connectivity across the life-span is anticipated. The exciting recent results in adult animals go some way in support of this premise; here VPA treatment reinstated critical periods and was shown to promote the ocular dominant plasticity as well as to permit visual acuity recovery consecutive to long-term monocular deprivation (Putignano et al., 2007).

5.4. "Chicken and egg" problem: some as yet unanswered questions in the story of VPA and juvenile myoclonic epilepsy?

Converging circumstantial human and animal data about putative effects of VPA on spatiotemporal myelination, brain plasticity behavior and cognition is abundant and repeatedly discussed in previous sections of this review. However, a firm 'naturalistic milieu substantiation of this proposed causal association is lacking in humans, with some work pointing to a minimal, if any effect of VPA treatment on cognition (Hessen et al., 2006; Vollmar et al., 2011). A group of patients that are historically commonly prescribed a longer term VPA treatment are those with IGE, and in particular men with JME are likely to get initiated on this medication (Perucca, 2002). It has now been consistently shown that patients with JME scored significantly below age, education and gender matched controls on neuropsychological measures of attention, immediate verbal memory, mental flexibility, control of inhibition, working memory, processing speed and verbal fluency (Deppe et al., 2008). Similar parameters, namely attention reaction time, speed of information processing, mild to moderate impairment of mental speed, psychomotor slowing, reduced visuo-motor function and verbal memory were all shown to be specifically affected by VPA treatment in number of studies (Hessen et al.

2006). In addition, some clinicians suggest that VPA withdrawal in chronic patients can lead to improved ability to perform activities that demanded rapid cognitive performance and complex motor coordination (Ristić et al., 2006; Lossius et al., 2008; Farkas et al., 2010). Of note are results of studies with recent onset pediatric JME patients (diagnosed within 12 months and predominantly on divalproex monotherapy) that showed an asymmetric and decelerated abnormal trajectory of fronto-thalamic growth in comparison to controls. This was shown to have important cognitive implications and a similar trajectory was sustained over a 2-year interval (Pulsipher et al., 2011). The authors argued against the possibility that the chronic duration of seizures was the mechanism behind the observed abnormalities but could not rule out the antiepileptic contribution to the recorded volumetric and neuropsychological executive effects.

By now a number of studies employing advanced imaging techniques in JME population confirmed abnormal brain connectivity in frontal regions corresponding to the anterior and ventral thalamic radiation (Deppe et al., 2008; Vulliemoz et al., 2011; O'Muircheartaigh et al., 2011; Vollmar et al., 2011). In addition to frontal lobe dysfunction, posterior brain regions abnormalities inclusive of connections of posterior callosal and cingulum connections to temporal cortex and posterior parietal regions were also implicated (Deppe et al., 2008; Vulliemoz et al., 2011; O'Muircheartaigh et al., 2011). An overall reduced supplementary motor area (SMA) structural connectivity, inclusive of its principal connections to the contralateral SMA, was shown in the tractography study of JME patients. It was suggested that this structural hypoconnectivity may functionally relate to previously noted impaired recruitment of motor cortical inhibition in JME (Vulliemoz et al., 2011). Another elegant functional neuroimaging study showed increasing coactivation of the primary motor cortex and the SMA region with increased cognitive demand in

JME patients (Vollmar et al., 2011). Additionally, an increased functional connectivity between the motor system and frontoparietal cognitive networks was demonstrated, perhaps suggesting the mechanism for the particular phenotype of JME, the myoclonic jerk and its facilitation through cognitive stressors. Variety of neuropsychiatric diseases (inclusive of SZ) show impaired deactivation of the default mode network during cognitive tasks and this was also established in JME patients (Vollmar et al., 2011). Although presumably the majority of JME patients in these studies were on VPA monotherapy, commonly no finite observations were made regarding its possible contribution to the noted changes in brain connectivity and structure. In one study a post hoc analysis showed a positive correlation between the daily VPA dose and the activity of bilateral frontal and parietal working memory network (Vollmar et al., 2011). It was argued that this effect may point to a 'normalizing' cognitive role for VPA in JME patients. However, the study design limitations did not allow for objective separation of drug effects from subject effects. An alternative explanation for these data could be that the same cognitive effort commands increased regional recruitment of otherwise less efficient neuronal networks possibly modulated by the higher doses of VPA. Previously argued putative effects of VPA on regional myelination and its role in brain plasticity may indeed account for some aspects of this observation.

In conclusion, recent neuroimaging studies of JME patients significantly advanced our knowledge of potential mechanisms behind the aberrant brain connectivity in this patient population but did very little in delineating any potential contributory drug effect. Many questions remain unanswered and some were additionally raised by these studies. Specifically, one of the important clinical questions in this patient group is about the possible covert modulatory effects of VPA treatment on the noted motor and cognitive abnormalities. Its effects on the brain connectivity in JME were hitherto not directly addressed by any of those studies.

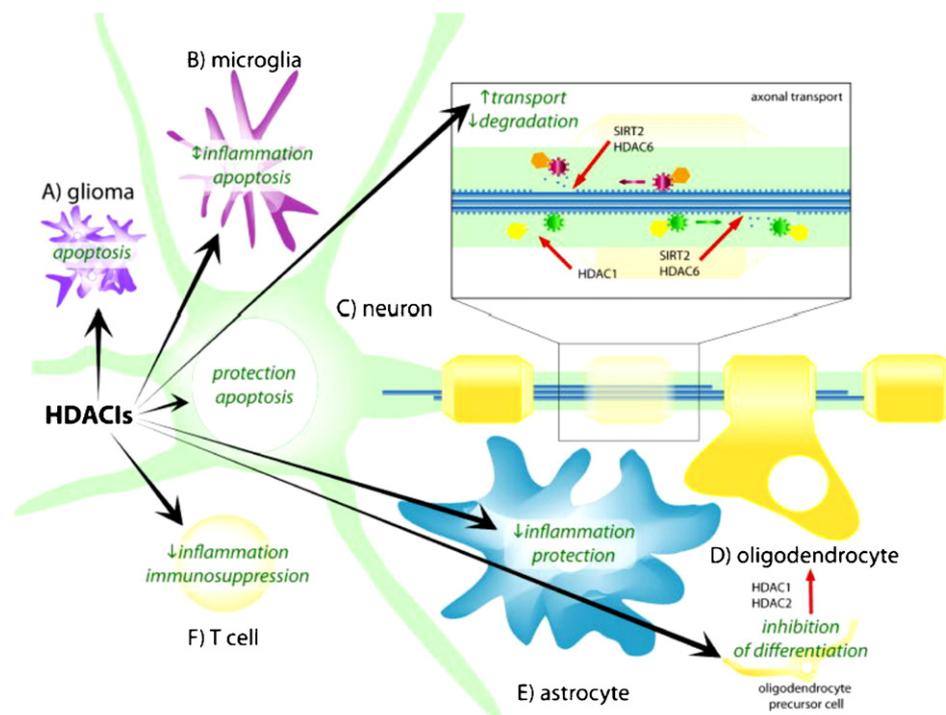


Fig. 3. Multicellular targets of HDACis are depicted. They can induce apoptosis in cancer cells (A); anti or pro-inflammatory effects in microglial cells (B); survival or apoptosis in neurons (C); inhibit the differentiation of oligodendrocyte progenitors (D); reduce inflammatory responses and induce protective effects of astrocytes (E); reduce inflammatory responses and induce immunosuppression in lymphocytes (F). Furthermore, HDACis may affect axonal transport (upper right inset). Deacetylation of tubulin inhibits both anterograde and retrograde transport; HDACis are thus able to restore transport.

Reproduced with permission from Dietz and Casaccia (2010), where a detailed discussion of HDACis actions can be found.

6. Conclusion and future directions

Heightened heterochronous periods of brain plasticity are recognized as essential for the developmental fine tuning of brain circuitry and various molecular and physical 'brakes', such as myelin, act to ensure against further aberrant development after an early sensitive period (Gogolla et al., 2009). The effects of drugs like VPA, that alter the epigenome, may under certain conditions reactivate critical periods and thus profoundly impact adult brain connectivity. Multimodal and later myelinating brain circuits involved in attention, executive function and behavior regulation are now thought to play a pivotal role in adult plasticity by their ability to modulate the coding efficiency of lower order networks, such as sensory-motor structures, during the attentional tasks (Gogolla et al., 2009; Bartzokis, 2011). Such top-down control of adult plasticity may allow fine-tuning of network connectivity by the environmental clues while at the same time maintain the overall circuit stability. Converging experimental and clinical data suggests possible an epigenetic modulatory role for VPA in many facets of this adult plasticity, many of which are beyond scope of this review (please refer to Fig. 3; Chuang et al., 2009; Nalivaeva et al., 2009; Dietz and Casaccia, 2010; Fischer et al., 2010).

The unique quality of human brain, which unlike that of any other primate, continues to undergo an orchestrated myelination process until late adulthood arguably lends itself to a theoretical construct where VPA epigenetic modulations should not be easily discarded. The advent of several new imaging techniques, inclusive of DTI and the myelin-specific MRI technique, mcDESPOt (Fig. 2B), provides a highly sophisticated platform through which in vivo visualization of any such effects of VPA on human myelin maturation can be attempted (Deoni et al., 2011). In order to competitively assess the clinical consequence of chronic use of this widely prescribed drug on connectivity, cognition, behavior and fronto-thalamic developmental trajectory prospective studies of age and gender matched JME patients should be assessed at various developmental snapshots and compared to those on other antiepileptics with negligent HDAC activity, such as Levetiracetam (Eyal et al., 2004). It is hoped that such longitudinal tractography sampling and assessment may capture any accelerated or decelerated development of distinct and time locked regional circuitry, possibly also allowing delineation of any later compensatory mechanisms from the original primary effect. Lastly, we believe that evidence assessed here also strongly argues for prudent chronic use of this antiepileptic in neuropsychiatric disorders (e.g. in BD, SZ). In pediatric and adolescent patient population, which may be particularly vulnerable to its accumulated prolonged effects, its use, in our opinion, might be better reconsidered until more is known of its effects, particularly where other evidence-based treatment alternatives are readily available.

Conflicts of interest

The authors do not have any conflicts of interest to report. The authors apologize to all the colleagues whose outstanding work could not be cited due to space limitations.

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