

Perspective

Formulating treatment of major psychiatric disorders: algorithm targets the dominantly affected brain cell-types

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Abstract

Background Pharmacotherapy for most psychiatric conditions was developed from serendipitous observations of benefit from drugs prescribed for different reasons. An algorithmic approach to formulating pharmacotherapy is proposed, based upon which combination of changed activities by brain cell-types is dominant for any particular condition, because those cell-types contain and surrogate for genetic, metabolic and environmental information, that has affected their function. The algorithm performs because functions of some or all the affected cell-types benefit from several available drugs: clemastine, dantrolene, erythropoietin, fingolimod, fluoxetine, lithium, memantine, minocycline, pioglitazone, piracetam, and riluzole

Procedures/findings Bipolar disorder, major depressive disorder, schizophrenia, Alzheimer's disease, and post-traumatic stress disorder, illustrate the algorithm; for them, literature reviews show that no single combination of altered cell-types accounts for all cases; but they identify, for each condition, which combination occurs most frequently, i.e., dominates, as compared with other possible combinations. Knowing the dominant combination of altered cell-types in a particular condition, permits formulation of therapy with combinations of drugs taken from the above list. The percentage of patients who might benefit from that therapy, depends upon the frequency with which the dominant combination occurs in patients with that particular condition.

Conclusions Knowing the dominant combination of changed cell types in psychiatric conditions, permits an algorithmically formulated, rationally-based treatment. Different studies of the same condition often produce discrepant results; all might be correct, because identical clinical phenotypes result from different combinations of impaired cell-types, thus producing different results. Clinical trials would validate both the proposed concept and choice of drugs.

Keywords Pharmacotherapy · Psychiatric disorders · Brain cell-types

1 Introduction

It is an old debate as to whether or not psychiatry is a branch of medicine or should be regarded as totally separate; also debated are queries concerning confidence in both diagnostic systems and treatment strategies [1, 2]. This article is not intended as a polemic in those debates but is aimed at a rational formulation of pharmacotherapy for patients whose cases receive only limited benefit from psychotherapy. It is relevant to note that effective pharmacotherapy for major psychiatric disorders commenced after serendipitous observations that chlorpromazine, originally produced and prescribed as an antihistamine, was seen to reduce symptoms of mania and schizophrenia; that imipramine, originally

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produced and prescribed as an antipsychotic, reduced depression; and that lithium reduced the excitability of guinea-pigs, leading to treatment of mania. Most subsequently developed antipsychotic drugs were based on those original observations, although a different approach was based upon the serotonin hypothesis and led to development of selective serotonin re-uptake inhibitors (SSRI). The serotonin hypothesis is now considered probably incorrect [3]; SSRI promotion of oligodendrocytes [4] and M2 microglia [5] is a possible basis for their efficacy in treating depression. During the past few decades, many research efforts have undertaken genetic studies of psychiatric disorders, in the expectation that their results might lead to rational drug development. Sullivan and Geschwind, however, stated that even with complete knowledge of the genetic architecture of a psychiatric disorder, full understanding requires knowing how loci interact in the nucleus, how gene and isoform expression are coordinated for many involved genes, and how all of these affect neural networks [6]. Likewise, in his editorial concerning genetic testing in psychiatry, Dubovsky pointed out that no genetic marker has yet been shown to be useful in prospectively identifying any specific psychiatric disorder [7]. Further, virtually every major psychiatric condition has a pathogenesis that involves genetic and metabolic impairments plus environmental factors; addressing them all requires an impractical number of medications. That task may be greatly simplified by the algorithmic approach to formulating treatment that is proposed here, because (1) there are only five major families of brain cell-types, i.e., astrocytes, oligodendrocytes, neurons, endothelial cells, and microglia, and all of them contain the genetic, metabolic and environmental factors that have affected their function; and (2) eleven available drugs, described below, benefit the cell-types that are dominantly affected in those psychiatric disorders that are discussed here to illustrate the approach.

2 The five families of cell-types in the brain

The following is a brief overview of the five families of cell-types in the brain. For several of them it is known that there are subtypes; but at this time there is little or no information about how pharmacotherapy affects those subtypes or their association with clinical outcomes. Acknowledging that the situation may change in the future when such data regarding subtypes becomes available, the present article, with a few exceptions, confines itself to the main families of cell-types and ignores the issue of subtypes. The cell-types are listed here uniformly, in the following order: astrocytes. Oligodendrocytes, neurons, endothelial cells, and microglia. Oligodendrocytes are always mentioned before neurons because if their numbers or functions diminish, then neurons and neural tracts suffer. Regarding endothelial cells: cerebral blood flow (CBF) is sometimes used as surrogate. For astrocytes. Oligodendrocytes, neurons, and endothelial cells, only down-regulation of their number or function is considered as pathogenic, since up-regulation is unlikely to have deleterious consequences; regarding microglia, it is up-regulation of number or function that is considered as most likely to have pathogenic consequences.

Astrocytes The high importance of astrocytes is shown by their accounting for approximately half the volume of the adult mammalian brain; that they provide the primary structural and trophic support for neurons; and that astrocyte processes ensheath neurons and capillaries. One astrocyte supports the functions of 3 or 4 neurons, and since each cortical neuron has approximately 38,000 synapses, processes from a single astrocyte can envelop approximately 150,000 synapses [8, 9]. The end feet of astrocyte processes, which contain aquaporin 4, also ensheath cerebral capillaries; aquaporin 4 must regulate that ensheathment, because aquaporin 4 knockout mice had ~60% less coverage of cerebral capillaries by astrocytic processes; for that reason, astrocytes regulate water permeability and, therefore, the transport of drugs across the blood–brain barrier (BBB) [10]. Other important functions of astrocytes are their uptake of the extracellular potassium from neural activity; their regulation of Ca²⁺ signaling and excitatory neurotransmitters; and their delivery of energy to neurons via the astrocyte–neuron lactate shuttle.

Oligodendrocytes A pool of undifferentiated oligodendrocyte precursor cells (OPC) remains in the adult CNS; they can differentiate into pre-myelinating and myelinating oligodendrocytes [11]. Myelination of axon is a major function of oligodendrocytes is myelination; its impairment would cause synaptic dysfunction, abnormal neural tracts, and disturbed cognition [12]. Phenotypic markers identify the lineage: OPC express platelet derived growth factor (PDGF); myelinating, mature oligodendrocytes express myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG); and both OPCs and mature oligodendrocytes share markers such as OLIG2. Mature oligodendrocytes express all three types of glutamate receptors—AMPA, kainate, and NMDA, making them subject to excitotoxic death. Stressors affect oligodendrocyte maturation, which impacts neurons. The prefrontal cortex (PFC) of mice housed in isolation had oligodendrocytes with shorter processes and less branching; they had fewer myelin genes (*MBP* and *MAG*); and electron microscopy showed reduced myelin thickness [13]. Liu et al. subjected mice to three different stressors, and showed

reduction of both myelin and oligodendrocyte gene transcripts [14]. Mice subjected to other mice that were aggressive, had significantly down-regulated genes that were myelin-related [15]; Banasr et al. subjected mice to a dozen different stressors, which resulted in a 39% reduction of oligodendrocytes [16].

Neurons need little elaboration since, obviously, their impairments are fundamental to the pathogenesis of almost every psychiatric condition. Already mentioned, a single astrocyte contacts thousands of synapses, and also the cerebral microvasculature [17]. In that way, there is a tricellular collaboration that incorporates neurons, astrocytes, and endothelial cells.

Endothelial cells The importance of endothelial cells is illustrated in the brain of AD patients, where string vessels, the remnants of capillary injury, are increased and vascular density is reduced (reviewed in ref [18]).

Microglia In the CNS, activated microglia may have a pro-inflammatory M1 phenotype or an anti-inflammatory M2 phenotype. M1 microglia produce cytokines and chemokines (IL-1 β , IL-6, IL-12, TNF- α , CCL2), express NADPH oxidase, and generate reactive oxygen species (ROS) and reactive nitrogen species; M2 microglia produce anti-inflammatory cytokines (IL-10, TGF- β), growth factors (IGF-1, FGF, CSF1), and neurotrophic growth factors [19]. A skewed M1 activation over M2 has been related to disease progression in AD [20], and is often involved in other psychiatric conditions.

3 Altered functional activity of dominant cell-types in selective psychiatric disorders used as illustrations

Although the concept suggested in this article is an algorithmic approach for formulation of pharmacotherapy of any psychiatric condition, five of those are considered for illustrative purposes. Decreases in either their number or activity, affecting astrocytes, oligodendrocytes, neurons, and endothelial cells, would predispose to disease, whereas for microglia, increase in their number or functional activity would predispose to disease; changes in opposite direction would likely not be deleterious and, therefore, are not mentioned here. Note that the determination of the dominant change in the brain cell-type is based upon the findings in citations provided by PubMed and Google Scholar, supplemented by those in key articles.

3.1 Bipolar disorder (BD)

Astrocytes Liu et al. [21] found increases in 3 reports, and decreases in 1.

Oligodendrocytes Liu et al. found no increases in any report and decreases in 2 [21], and Uranova et al. saw a 29% decrease [22].

Neurons Gigase et al. summarized autopsies showing increased neurons in six and decreased neurons in nine [23]. In the dorsolateral (dl) prefrontal cortex (PFC) of BD, Rajkowska et al. saw reduced neuronal density in layers III and V (16% and 30%, respectively) [24]. Summarizing 12 reports, Cotter et al. found smaller neuronal size in layers 5 and 6 of the dlPFC [25]. Other studies of the dlPFC in BD, showed increased neurons in 1 [26] and decreases in 12 [27–38].

Interneurons Gigase et al. summarized reported studies of BD brains, showing interneurons as increased in one brain region, and decreased in sixteen [23].

Endothelial cells Kruger et al. measured CBF by using [150] H₂O and PET scanning [39]. Subjects drafted a brief script describing a sad life event; the script was projected onto a computer screen during the PET scan; CBF was measured in baseline euthymia and in provoked sadness. Decreased CBF in the ventromedial (vm) PFC distinguished BD patients from their at-risk siblings. Another study used breath-holding, which should produce decreased cerebral oxygenation and cerebral vasodilatation. Twenty-five adolescents with BD and 25 psychiatrically healthy controls completed six 15-s breath-holds during functional magnetic resonance imaging, and cerebrovascular reactivity (CVR) was determined by comparing blood-oxygenation-level dependent signal changes [40]. During breath-holding, CVR in several brain regions was decreased in BD versus controls.

A systematic review by Toma et al., yielded 33 studies, 118 subjects with BD/depression, 46 with BD/mania, 24 with BD/euthymia, and 385 controls [41]. CBF in multiple brain areas was reduced in all BD subjects except 22 who had increased flow. However, discrepant results were found by Zeng et al., who saw no difference in CBF, as assessed by arterial spin labelling, in 61 patients with BD [42].

Microglia Liu et al. found increases in 1 report and decreases in 2 [21].

Summary: the dominant changes in brain cell-type in BD are decreases in oligodendrocytes, neurons, and endothelial cells.

3.2 Major depressive disorder (MDD)

Astrocytes In MDD, Liu et al. saw increases in 3 reports and decreases in 11 [21]; Oh et al. gave evidence for reduced numbers of astrocytes causing reduced uptake of glutamate from the synaptic cleft [43]; and Chandley et al. noted a robust decrease of astrocytic gene expressions [44].

Oligodendrocytes In single reports, Liu et al. found both increases and decreases of oligodendrocytes [21]. In MDD, Aston et al. saw significantly decreased expression of 17 genes related to oligodendrocyte function [45]. Rajkowska et al. noted decreased oligodendrocyte somal size in the white matter of the ventral PFC [46].

Neurons Several reports showed decreases in neuronal numbers [22, 35, 43, 47, 48]. One study showed a difference according to the presence or absence of early life adversity (ELA); MDD subjects who had suicided and also had exposure to ELA, had increased numbers of granule neurons in the dentate gyrus (DG) whereas without such ELA exposure there were fewer neural progenitor cells in the DG [49].

Endothelial cells Several reports show decreased cerebral blood flow in MDD [50–54].

Microglia Liu et al. saw increases in 5 reports and decreases in 1 [21].

Summary: the dominant changes in brain cell-type in MDD are decreases in astrocytes, oligodendrocytes, neurons, and endothelial cells, and increases in microglia.

3.3 Schizophrenia

Astrocytes may be increased in SCZ [55, 56] but are sometimes decreased [57].

Oligodendrocytes may be decreased in SCZ [58, 59]; a systematic study showed reduced levels in 15 of 25 reports [21].

Neurons are usually decreased in SCZ [60], with GABAergic neurons in the PFC fewer by 40% [61] (OK), non-pyramidal cells reduced by 40% in the hippocampal CA2 [62] (OK), and hippocampal neurons with reduced somal size [63].

Endothelial cells are often decreased in SCZ [64].

Microglia are usually increased in SCZ [65].

Summary: the dominant changes in brain cell-type in SCZ are decreases in oligodendrocytes, neurons and endothelial cells, and increases in microglia.

3.4 AD

Astrocytes in AD. Emphasizing their importance for cognition, astrocyte numbers in the dentate gyrus were more reduced in Braak stages 3–4 than in stages 0–2 [66]; and because astrocyte processes wrap around cerebral microvasculature, the morphological modifications of astrocytes affect micro-cerebral blood flow [67] and, therefore, neural function [68].

Oligodendrocytes in AD. Mature oligodendrocytes perform myelination of naked axons; if their numbers are decreased, e.g., from impaired maturation of oligodendrocyte precursor cells (OPC), so that myelination becomes inadequate, then neural tracts suffer and cognition may be disturbed [68]. Exposure of oligodendrocyte cultures to 1 μM of $\text{A}\beta_{1-42}$ induced cell death; morphological changes, e.g., shrunken cell bodies and a breakdown of their processes; and an 3.2-fold increase of lactate dehydrogenase activity released to the culture media [69].

Neurons in AD AD patients with severe tau pathology had a decreased number of newly generated neurons in their dentate gyrus [66]. Leng et al. found a selectively vulnerable subpopulation of excitatory neurons in the entorhinal cortex (EC) and showed a depletion of this subpopulation during AD progression [70].

Endothelial cells in AD Microvascular disease affects the progression of cognitive deficits in AD [71]. Endothelial cells contain the scavenger receptor, CD36, whose interaction with $\text{A}\beta$ activates NADPH oxidase, producing vascular oxidative stress and neurovascular dysregulation [72]. String vessels, the remnants of destroyed microcapillaries, are seen throughout the brain of AD [18]. In addition, microinfarcts, with minute foci of neuronal loss as small as 50 μm , were seen in 43% of AD brains [73].

Microglia in AD Several reports concerning the role of microglia in AD are conflicting, the likely reason being the need to distinguish between proinflammatory and anti-inflammatory microglia, because a skewed M1 activation over M2 has been related to disease progression in AD [20], and this is the dominant but not universal change in AD.

Summary: the dominant changes in brain cell-type in AD are decreases in astrocytes, oligodendrocytes, neurons and endothelial cells, and increases in microglia.

3.5 PTSD

Astrocytes: Gill et al. assessed astrocyte levels in PTSD and found them decreased [74]. Chronic stress in rats reduced the length and volume of astrocytic processes by 40.6% and 56%, respectively, and the number of their branch points was reduced by 57.8% [75].

Oligodendrocytes: Brains from females with PTSD had down-regulated oligodendrocyte-associated genes (*MBP* and *MBOP*) [76]. Bonnefil et al. showed that social defeat stress in mice reduced mature oligodendrocytes by 31.8% [77]. In another study they showed that chronic variable stress produced down-regulation of oligodendrocyte specific genes in the nucleus accumbens (NAcc) and PFC but upregulation in the corpus callosum [78]. Banasr et al. caused unpredictable stress in rats; after 15 days, the prelimbic cortex had 21% fewer oligodendrocytes [16]. After traumatic brain injury in rats, numbers of oligodendrocytes decreased significantly [79].

Neurons: Smith et al. produced fear conditioning in mice, causing reduced density of dendritic spines of pyramidal neurons in the hippocampus and medial PFC [80].

Endothelial cells: Brains from persons with PTSD had up-regulated endothelin1 gene, *EDN1*, cells in the vmPFC, which would decrease cerebral microvascular flow [76]. After traumatic brain injury in mice, there was a 1.5-fold increased apoptosis of cerebrovascular endothelial cells and increased BBB permeability [81].

Microglia: Fear conditioning also increased the length of microglial processes [80]. Rats whose behavior was severely disturbed by the scent of predators, had increased hippocampal microglia [82]. After single, prolonged stress, even minimal pain induced activation of hippocampal microglia [83].

Summary: the dominant changes in brain cell-type in PTSD are decreases in astrocytes, oligodendrocytes, neurons, and endothelial cells, and increases in microglia.

4 Eleven available drugs benefit some or all of the five cell-types. Descriptions of their actions are deliberately brief: interested readers may consult the source citations for further information. N.B., use of any one of the following drugs for the purposes suggested in this article, would be off-label use

Highly abbreviated descriptions for likely therapeutic effects are provided here, showing either an increase that the drugs induce in number or activation of astrocytes, oligodendrocytes, synapses and neurons, and endothelial cells; or a decrease in number or activation of microglia.

Clemastine decreased loss of astrocytes [84]; increased postsynaptic proteins [84], muscarinic receptor, synapsin 1 and Homer 1, and improved oligodendrocyte survival/function [85, 86]; it enhanced myelin repair [87] and neuronal function [88]; it enhanced myelination in the PFC [14, 89]; it also enhanced visual function [86, 90]. Clemastine provided mitochondrial protection [91, 92]; and suppressed microglial M1 activation [93].

Dantrolene, by antagonizing ryanodine receptors and blocking Ca^{2+} release, prevents glutamate-caused increase in astrocytic volume [94], oligodendrocyte death [92], and preserves synaptic and neural function. Several other mechanisms for neuroprotection by dantrolene are in refs [95–106]. A potential adverse effect is on cerebral microvasculature, because release of BDNF requires Ca^{2+} mobilization [107].

Erythropoietin (EPO) increased differentiation of neuronal stem cells (NSC) into astrocytes [108]; increased oligodendrocytes [108], and neurons and dendritic spines [109] via increased production of brain-derived neurotrophic factor (BDNF) and its receptor [110]; and by enhancing differentiation of NSC [111]. EPO improved function of synapses, [112–114], endothelial cells [115, 116] and microglia [117].

Fingolimod an agonist of sphingomyelin phosphate (S1P), produces cell proliferation [118]. In astrocytes, fingolimod activated neurotrophic genes [119], and reduced formation of ceramide that causes apoptosis [120, 121]. It activated myelinating oligodendrocytes [122] increased OPCs, myelination, and neurological function [123], and

ameliorated brain demyelination [124]. It enriched synaptic genes [125], prevented synaptic toxicity [126], and reversed synaptic hypersensitivities (123). It produced myelin in demyelinated brain [127], and prevented neural death from NMDA [128]. In multiple sclerosis, it improved axonal and myelin integrity [129]; and in mice prevented demyelination [130]. It increased dendritic spines [131, 132], reduced neuronal death from ROS [133], and improved mitochondrial production of ATP [134]. In microglia, fingolimod shifted M1 polarization toward M2 [135, 136].

Fluoxetine induced increases in: astrocytes [137], oligodendrocytes [138–140], neurons [138–140], endothelial cells [141], and decreased microglial activation [140, 142, 143].

Fluoxetine activates astrocytes to produce BDNF [137, 144, 145], and promotes clearance of astrocytes with damaged mitochondria [146]. It up-regulated OPC and oligodendrocyte markers [138], and reduced oligodendrocyte senescence [147]. Fluoxetine increased neurogenesis [138, 148], neuronal circuits [149], and spatial learning [150]. Neurons deprived of glucose and oxygen, had increased survival with fluoxetine [151]. It increased vasodilatation via differentiation and proliferation of endothelial cells and decreased arteriolar tone [141, 152]. In microglia, it attenuated NADPH oxidase activation, production of ROS and reactive nitrogen species, and down-regulated M1 and up-regulated M2 activation [5, 142, 153].

Lithium doubled astrocytic numbers and their VEGF secretion [154]. Oligodendrocyte expression of PLP and MBP increased, improving synaptic and neuronal function [155–159]. By negating activation of GSK-3 β , synaptic expression of PSD-95 and gephyrin were enhanced. Lithium promoted neurogenesis [159–162]; doubled BDNF levels, increased dendritic length, increased anti-apoptotic Bcl2 and Bcl-x_L, and prevented neuronal death from glutamate and pro-apoptotic BAD, BAX, and caspase 3 [163]. It increased numbers and size of neural mitochondria [164], increased antioxidants [157, 164], minimized neurotoxicity from cytochrome c, and promoted mitochondrial biogenesis [165, 166]. Lithium benefitted microvasculature by increasing VEGF secretion [167] and BBB integrity [168]. Lithium's inhibition of GSK-3 β , reduced production and activation of pro-inflammatory mediators [169–171].

Memantine induced activation of astrocytes [172], and prevented losses of oligodendrocytes [173], synapses and neurons [174–176], and endothelial cells [177]. It is a NMDAR antagonist, enters the NMDAR's Ca²⁺ channel and decreases its permeability, so prevents neuronal excitotoxicity and death [174]. Memantine provides synaptic protection via several mechanisms (183,184,185,186,187): preventing cytotoxicity by blocking inhibition of a guanine triphosphatase involved in multiple cellular processes, thus protecting against mitochondrial dysfunction causing cell death via cytochrome c release, ROS and peroxide production [178–181]. Blocking the ion channel of the acetylcholine receptors also prevents neurotoxicity [182]. Memantine benefitted brain endothelial cells and blocked disruption of the BBB [183].

Minocycline prevented oligodendrocyte toxicity caused by deprivation of oxygen and glucose [184], microglial-induced apoptosis [185], by minocycline preventing inhibition of CREB's up-regulation [186] and caused by A β [187]. Synaptic function improved from increased levels of PSD-95 and dendritic spines [188]. It prevented cognitive decline caused by an antagonist of the NMDAR [189]. Neuronal benefit was also from its increased expression of BDNF, CREB, and phospho-CREB [186], and proliferation of NPCs [190]. Minocycline potentiated neurite outgrowth [191]. In a transgenic mouse model of Down's syndrome, minocycline prevented decline of cholinergic neurons [192]. In a list of 1040 drugs that prevent release of cytochrome c, minocycline was the second most potent [193], the mechanism involves inhibiting mitochondrial increases in Ca²⁺ concentration plus inhibition of NADH-cytochrome c reductase and cytochrome c oxidase [193, 194]. Finally, minocycline prevented microglial activation [195, 196].

Pioglitazone, a PPAR γ agonist, prevents phosphorylation of JAK-STAT in astrocytes and thereby induces increases in neurons [197, 198], oligodendrocytes [153, 198], endothelial cells [199], and decreases in microglia [200]. Ciglitazone and curcumin, also PPAR γ agonists, were cytoprotective for astrocytes and reversed their decreased expression of PPAR γ receptor after exposure to A β ₂₅₋₃₅ [201, 202]; and ciglitazone increased formation of oligodendrocyte progenitors [198]. Pioglitazone rescued the demyelination caused by anti-MOG autoantibody [203]. The promotion of OPC differentiation into mature oligodendrocytes by IL-4 was mediated by PPAR γ or curcumin [204, 205]. PPAR γ agonism increases the neurogenic differentiation gene, *NeyroD1* [198], and protected cortical neurons and axons against toxicity induced by NO or KCl-induced toxicity [197, 206].

PPAR γ also produces endothelial cell proliferation, and angiogenesis [199, 207]. In microglia, PPAR γ agonists inhibit cytokine production by down-regulating proinflammatory genes(211). In addition, rosiglitazone up-regulated M2 microglia [208].

Piracetam increased numbers and function of astrocytes [209]. It also increased function of synapses [210–213] and neurons [210]: it decreased neurotoxicity from deprivation of oxygen and glucose, hypoperfusion, ethanol feeding or ethanol withdrawal [211, 214–216] It also caused longer neurites [210]. The effects of piracetam may derive in part

from the restoration of cell membrane fluidity induced by a conformational change in the phospholipids of liposomal membrane [213]

By decreasing mitochondrial swelling and permeability caused by excessive Ca^{2+} opening the MPTP, it improved mitochondrial membrane potential and ATP levels, shifted the balance of mitochondrial fission or fusion towards fusion, and reversed the adverse effect of pro-oxidants [217]. Additionally, it reversed the cytotoxic effects of p53 and BAX [211].

Riluzole increased both the gene for the excitatory amino acid transporter (EAAT2) and its expression, thus enhancing glutamate uptake by astrocytes, and protecting against excitotoxicity of neurons [218, 219]. It benefits synapses, by inhibiting voltage-activated sodium currents which prevents reverse operation of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger [220], and by increasing LTP [221]. It caused a 40-fold increase in hippocampal BDNF, creating neurogenesis [222]; and protected against neural degeneration caused by ischemia [223]. N-acetylaspartate is exclusively expressed in neurons and was increased in the cerebral cortex by exposure to riluzole [224]. In neurons, it also decreased oxidative stress, lipid peroxidation, and ATP depletion [225, 226]. Microglial activation was ameliorated by riluzole [227], which also upregulated the mRNA levels of M2 markers and downregulated those of M1 markers [228].

5 Drugs that might be therapeutically beneficial in a reasonable number of patients, by addressing the dominantly affected cell-types in BD, MDD, SCZ, AD, and PTSD

For BD, increasing oligodendrocytes, neurons and endothelial cells (CBF), is achieved by erythropoietin, fluoxetine, lithium, memantine, and pioglitazone.

For MDD, increasing astrocytes, oligodendrocytes, neurons, and endothelial cells (CBF), and decreasing microglia, is achieved by erythropoietin, fluoxetine, lithium and pioglitazone.

For SCZ, increasing oligodendrocytes, neurons, and endothelial cells (CBF), and decreasing microglia, is achieved by erythropoietin, fingolimod, fluoxetine, lithium, and pioglitazone.

For AD, increasing astrocytes, oligodendrocytes, neurons, and endothelial cells (or CBF), and decreasing microglia, is achieved by erythropoietin, fluoxetine, lithium and pioglitazone.

For PTSD, increasing astrocytes, oligodendrocytes, neurons, and endothelial cells, and decreasing microglia, is achieved by erythropoietin, fluoxetine, lithium and pioglitazone.

5.1 Shared dominant cell-types between disorders

There are shared changes in dominant cell-types between some psychiatric conditions, from which one may infer shared pathogenesis and similar treatments. Thus, MDD, AD, and PTSD, share decreases in astrocytes, oligodendrocytes, neurons, and endothelial cells, and increases in microglia. SCZ has decreases in oligodendrocytes, neurons, and endothelial cells, and increases in microglia, so shares these features with MDD, AD, and PTSD. Evidence of an overlapping genetic risk that is similar to their overlapping of affected cell-types, was shown for MDD and AD by Lutz et al. [229], between PTSD and schizophrenia by Duncan et al. [230], and between MDD and schizophrenia by The Psychiatric Genomics Consortium [231]. That consortium demonstrated significant genetic correlations between SCZ and BD (0.68), MDD and BD (0.47), SCZ and MDD (0.43), and was non-significant between psychiatric disorders and the negative control, Crohn's disease. The foregoing genetic data support the concept proposed in this article, that brain cell-types, may be used as surrogates for all of the genetic, metabolic, and environmental, data for the inputs of which they are storehouses.

5.2 APOE4 affects functions of astrocytes, oligodendrocytes, neurons, endothelial cells, and microglia

Further support for the concept that brain cell-types may be used as surrogates for several abnormalities affecting their function, comes from brain cell-types that carry APOE4. The APOE4 variant of the *APOE* gene product, renders its carriers susceptible to AD. One mechanism for this may be its effect on the five families of brain cell-types. Blanchard et al. reported several such effects: that cholesterol transport was defective in oligodendrocytes derived from induced pluripotent stem cells (iPSC) carrying APOE4; that these APOE4+oligodendrocytes accumulated cholesteryl ester species; and that this was associated with down-regulation of genes linked to myelination and decreased production of MBP [232]. Lin et al. showed that the APOE4 variant can also lead to extensive gene expression alterations in neurons, astrocytes, and microglia; APOE4 astrocytes had cholesterol accumulation, and APOE4 microglia-like cells had increased up-regulation of genes associated with immune responses and inflammation [233]. Lipid accumulation in APOE4+microglia was seen also by Victor et al.; and,

as compared with that of APOE3 microglia, the pro-inflammatory activity of APOE4+microglia was exacerbated by medium from neuronal cultures, demonstrating cross-talk between neurons and APOE4+microglia [234]. APOE4+endothelial cells had dysfunctions in pathways leading to blood clotting factors and inflammation [235]. Finally, removal of APOE4 from astrocytes led to improvements in synaptic function with increase in PD95, neurons, oligodendrocytes, and microglia [236]. Thus, all the foregoing data suggest that one of the several mechanisms accounting for the association between APOE4 and AD, is that APOE4 detrimentally affects the functions of astrocytes, oligodendrocytes, synapses, neurons, endothelial cells, and microglia, which supports the thesis of this article, that treatments should be directed to improving the functions of affected brain cell-types.

5.3 Adverse effects

The choice of a medication is partly determined by its safety profile, particularly for serious adverse events (SAEs), less so for minor adverse events (AE). Following are summaries of reports of SAEs for the above drugs.

Clemastine: no SAEs seen in several clinical trials.

Dantrolene: other than caused by preexisting disease, SAEs were rare [237].

Erythropoietin: only 3 of 50 studies attributed SAEs to erythropoietin but those used very high-dosages (> 200,000 IU) [238]. If chosen for use in patients with BD, MDD, or SCZ, erythropoietin should be low dosage, 10,000 IU given IM once monthly.

Fingolimod: pooled data from 1640 subjects, showed that fingolimod 0.5 mg gave transient, usually asymptomatic, second-degree heart block, on treatment initiation; minor BP increases; generally asymptomatic liver enzyme elevations (9%); and macular oedema (0.4%) [239]. Higher doses (1.25 mg) gave more frequent SAEs. In patients with BD, MDD, SCZ, AD, dosage should be only 0.5 mgs daily.

Fluoxetine: Beasley et al. obtained data from 25 double-blind clinical trials involving 4016 patients with MDD randomized to treatment that included fluoxetine 20 to 80 mg/d [240]. At a dose of 20 mg/d, fluoxetine-treated patients had a discontinuation rate due to adverse events that was not statistically significantly different from that in placebo recipients. Nevertheless, although in this article the suggested dose is only 10 mg/d in combination with lithium, caution is necessary because the possibility exists of inducing mania, even though that is reported mainly with doses of ≥ 20 mg/day [241].

Lithium: SAEs, include hypercalcemia, hypothyroidism [242], nephrogenic diabetes insipidus, and renal insufficiency [243]. Low dosage (< 100 mgs daily) benefited Alzheimer's dementia; thus 75 mg daily might be an appropriate dose in BD, MDD, SCZ, AD or PTSD. It should not be used if glomerular filtration rate is < 60 mL/min.

Memantine: no significantly increased SAEs [244].

Minocycline: a review showed six patients with a hypersensitivity syndrome, six with serum sickness, and 24 with drug-induced lupus [245]. Minocycline has been used in thousands of persons over many years, so SAEs are rare. ANA test should be negative before prescribing it.

Piracetam: a large study, did not show more SAEs than with placebo [246].

Riluzole: nine studies did not show increased SAEs [247].

5.4 The need for clinical trials

Clinical trials would demonstrate validity of both the proposed concept and the choice of drugs for treatment; and would also show the percentage of patients benefitting from the chosen combination of drugs administered for a particular psychiatric condition. In a clinical trial that randomly assigns participants to receive active drugs or placebo, the primary objective would be to show $\geq 30\%$ better results from active drugs than from placebo. In order to provide deeper coverage and lower dosages, two drugs rather than one should be used.

6 Discussion

The proposed model is a basis for formulating treatment of major neuro- psychiatric conditions. The model overcomes the problem of addressing the many genetic, mitochondrial, and metabolic impairments associated with the discussed conditions; it proposes drugs that address the dominant combination of brain cell-types, which simplifies use of known data; future availability of data that involve subtypes of brain cell-types, will allow improvement of the model. Drugs are discussed which address the brain's five cell-types that affect the occurrence of BD, MDD, SCZ, AD, and PTSD.

It is acknowledged that a single treatment combination would not benefit all patients with a particular psychiatric phenotype, because an identical clinical phenotype may result from several, different combinations of cell-types, only one of which is dominant compared with the other as compared with the others; thus, the suggested treatments would benefit only those subjects whose condition is caused by a particular set of dominant cell-types. Nevertheless, benefit to even 20–30% of patients would be clinically useful. It is, also, worth noting that in studies of all of the mentioned conditions, ‘conflicting’ results are reported; yet because an identical clinical phenotype may incorporate different combinations of cell-types, it is possible that the different results might not be actually ‘conflicting’ but correct.

The determination of the dominant change in the brain cell-type in any particular condition is based upon the findings in published reports and, thus, the diligence with which the literature is reviewed. Data for the present article were derived primarily from citations provided by PubMed and Google Scholar. Citations found in key articles are often very relevant; for example, ref [60] cited an article that reviewed studies in 1415 patients with SCZ [248]. For the four psychiatric conditions used to illustrate the proposed approach, the 61 citations included seven that reviewed 1136 separate, published reports [21, 23, 37, 41, 56, 60, 68], and one that reviewed 15 publicly available data sets [37]. Reviews generally refer to very large numbers of subjects; e.g., one “review of reviews” analyzed 683 reports in 26 reviews involving 55,561 patients [65].

It is relevant to ask, ‘which is primary, alterations in brain cell-types or the changed behavior?’ because if it is the altered behavior that causes the changes in brain cell-types, then addressing the changes in those cells would not affect behavior. However, and fortunately for the thesis of this article, a number of studies show that the altered brain cells precede the altered behavior. In one such study, Santarelli et al. noted that chronic antidepressant treatments increase adult hippocampal neurogenesis; they found that destruction by X-irradiation of the region of mouse brain containing the hippocampus, prevented both the neurogenesis and the behavioral benefits of two classes of antidepressants, showing that stimulation of neurogenesis in the hippocampus underpins the behavioral effects of chronic antidepressants [249]. Related to that, the induction of depression-like behavior in chronic stress models was associated with elimination of postsynaptic dendritic spines and a loss of PFC projection neurons [250]; and ablation of astrocytes in the PFC, which deprives neurons of trophic support, increased anhedonia, anxiety, and helplessness, similar to the depression-like behaviors caused by chronic unpredictable stress [251]. The above studies may be interpreted as demonstrating that, for the relationship between neurons and behavior, it is the neuronal action that precedes a behavioral change, not vice versa.

There are, of course, many caveats to consider: (1) Cell-type families have sub-types; therefore, designating a drug as addressing a generic cell-type may be inaccurate. However, there are scores of subtypes. E.g., Tasic et al. found 56 glutamatergic and 61 GABAergic, cortical neuronal subtypes [252], and Bickoff et al. documented multiple subtypes of spinal, inhibitory interneurons [253]. Currently, data are sparse concerning the presence and distribution of cell-subtypes in the major psychiatric conditions, and there is no information regarding a possible, differential effect of medication upon subtypes. In future, when more information about them becomes available, it will be possible to establish if subtypes must be separately accounted for. (2) One report found no consistent evidence of astrocytic impairments in 11 psychiatric disorders; that study determined cell-type by using single cell transcriptomic data integrated with genome wide association study results [254]. However, there is variability of gene expression by astrocytes, e.g., Stahlberg et al. identified two subpopulations of astrocytes with distinct gene expression profiles [255]. Thus, absence of either a specific gene or set of genes would incorrectly label some cells as being ‘not astrocytes’. Further, glial fibrillary acidic protein (GFAP) is the cardinal cytological marker of astrocytes but GFAP-negative astrocytes also exist, e.g., Tatsumi et al. saw that brain regions such as the basal forebrain, thalamic nuclei, and deep cerebellar nuclei, tended to lack GFAP-positive astrocytes [256]; thus also in this case, the absence of GFAP would incorrectly identify cells as being ‘not astrocytes’. (3) Another limitation of the proposed algorithm is that it assumes uniform changes of cell-types across all brain regions. That this is not necessarily the case, is exemplified by observations made by Gandal et al. in brains from patients with autistic spectrum disorder (ASD) [257]. They saw a regional gradients, with three-fold to four-fold more differentially expressed genes in cell-types (particularly excitatory neurons, interneurons, and oligodendrocytes) in occipital and parietal cortices than in the PFC.

Despite these theoretical limitations there is, nevertheless, theoretical consistency in that the proposed target of therapy is the changed direction of number or function of the individual cell-types as seen in individual psychiatric conditions. The accuracy of the cell-type(s) as target can be tested by clinical trial since knowing the changed direction of cell-types provides clinical benefit if a specific drug or combination of drugs corrects both the changed direction and the clinical condition.

7 Conclusion

1. For most psychiatric conditions, pathogenesis depends on impairment of either number or function among the five families of cell-types in the brain. Cell-types are storehouses of and, therefore, surrogates for, pathogenically important genetic, metabolic, and environmental inputs. The dominantly changed cell-types in a given condition permits algorithmic formulation of a pharmacotherapeutic regimen.
2. Because an identical clinical phenotype may result from different combinations and permutations of impaired cell-types, no single combination of cell-types accounts for all cases; in a given set of subjects one can only discern the combination that is dominant as compared with the others; therefore, different studies may produce discrepant results, all of which could be accurate.
3. Eleven drugs are presented that benefit either all or some of the five cell-types and from among which treatment may be formulated for each condition.
4. Clinical trial is required to validate both the proposed concept and choice of drugs.

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Author contributions JF formed the concept, performed the research, wrote and reviewed the article. The author read and approved the final manuscript.

Data availability Data regarding the suggested drugs are available from the author.

Declarations

Competing interests The authors declare no competing interests.

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References

1. Guze SB. Why psychiatry is a branch of medicine. Oxford: Oxford University Press; 1992.
2. Stoyanov DS, Di Nicola V. Psychiatry in crisis: epistemological and ontological concerns. *Am J Psychiatry Neurosci.* 2017;5:6.
3. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry.* 2022. <https://doi.org/10.1038/s41380-022-01661-0>.
4. Fan LW, Bhatt A, Tien LT, Zheng B, Simpson KL, Lin RC, et al. Exposure to serotonin adversely affects oligodendrocyte development and myelination in vitro. *J Neurochem.* 2015;133:532–43.
5. Su F, Yi H, Xu L, Zhang Z. Fluoxetine and S-citalopram inhibit M1 activation and promote M2 activation of microglia in vitro. *Neuroscience.* 2015;294:60–8.
6. Sullivan PF, Geschwind DH. Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. *Cell.* 2019;177:162–83.
7. Dubovsky SL. The limitations of genetic testing in psychiatry. *Psychother Psychosom.* 2016;85:129–35.
8. Cragg BG. The density of synapses and neurons in normal, mentally defective ageing human brains. *Brain: J Neurol.* 1975;98:81–90.
9. Agulhon C, Petravic J, McMullen AB, Sweger EJ, Minton SK, Taves SR, et al. What is the role of astrocyte calcium in neurophysiology? *Neuron.* 2008;59:932–46.
10. Di Benedetto B, Malik VA, Begum S, Jablonowski L, Gómez-González GB, Neumann ID, et al. Fluoxetine requires the endfeet protein aquaporin-4 to enhance plasticity of astrocyte processes. *Front Cell Neurosci.* 2016;10:8.
11. Roggeri A, Schepers M, Tiane A, Rombaut B, Van Veggel L, Hellings N, et al. Sphingosine-1-Phosphate Receptor Modulators and Oligodendroglial cells: beyond Immunomodulation. *Int J Mol Sci.* 2020;21:7537.
12. Mei F, Wang H, Liu S, Niu J, Wang L, He Y, et al. Stage-specific deletion of Olig2 conveys opposing functions on differentiation and maturation of oligodendrocytes. *J Neurosci.* 2013;33:8454–62.
13. Makinodan M, Rosen KM, Ito S, Corfas G. A critical period for social experience-dependent oligodendrocyte maturation and myelination. *Science.* 2012;337:1357–60.

14. Liu J, Dietz K, DeLoyht JM, Pedre X, Kelkar D, Kaur J, et al. Impaired adult myelination in the prefrontal cortex of socially isolated mice. *Nat Neurosci*. 2012;15:1621–3.
15. Lehmann ML, Weigel TK, Elkhoulou AG, Herkenham M. Chronic social defeat reduces myelination in the mouse medial prefrontal cortex. *Sci Rep*. 2017;7:1–13.
16. Banasr M, Valentine GW, Li X-Y, Gourley SL, Taylor JR, Duman RS. Chronic unpredictable stress decreases cell proliferation in the cerebral cortex of the adult rat. *Biol Psychiatry*. 2007;62:496–504.
17. Halassa MM, Haydon PG. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annu Rev Physiol*. 2010;72:335–55.
18. Fessel W. Concordance of several subcellular interactions initiates Alzheimer's dementia their reversal requires combination treatment. *Am J Alzheimer's Dis Demen*. 2017;32:166–81.
19. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol*. 2017;35:441–68.
20. Hansen DV, Hanson JE, Sheng M. Microglia in Alzheimer's disease. *J Cell Biol*. 2018;217:459–72.
21. Liu S-H, Du Y, Chen L, Cheng Y. Glial cell abnormalities in major psychiatric diseases: a systematic review of postmortem brain studies. *Mol Neurobiol*. 2022. <https://doi.org/10.1007/s12035-021-02672-8>.
22. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res*. 2004;2:269–75.
23. Gigase FA, Snijders GJ, Boks MP, de Witte LD. Neurons and glial cells in bipolar disorder: a systematic review of postmortem brain studies of cell number and size. *Neurosci Biobehav Rev*. 2019;103:150–62.
24. Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry*. 2001;49:741–52.
25. Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex*. 2002;12:386–94.
26. Connor CM, Guo Y, Akbarian S. Cingulate white matter neurons in schizophrenia and bipolar disorder. *Biol Psychiatry*. 2009;66:486–93.
27. Benes FM, Vincent SL, Todtenkopf M. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biol Psychiatry*. 2001;50:395–406.
28. Guidotti A, Auta J, Davis JM, Gerevini VD, Dwivedi Y, Grayson DR, et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry*. 2000;57:1061–9.
29. Pantazopoulos H, Lange N, Baldessarini RJ, Berretta S. Parvalbumin neurons in the entorhinal cortex of subjects diagnosed with bipolar disorder or schizophrenia. *Biol Psychiatry*. 2007;61:640–52.
30. Fatemi S, Earle J, McMenomy T. Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. *Mol Psychiatry*. 2000;5:654–63.
31. Konradi C, Zimmerman EI, Yang CK, Lohmann KM, Gresch P, Pantazopoulos H, et al. Hippocampal interneurons in bipolar disorder. *Arch Gen Psychiatry*. 2011;68:340–50.
32. Liu L, Schulz SC, Lee S, Reutiman TJ, Fatemi SH. Hippocampal CA1 pyramidal cell size is reduced in bipolar disorder. *Cell Mol Neurobiol*. 2007;27:351–8.
33. Berretta S, Pantazopoulos H, Lange N. Neuron numbers and volume of the amygdala in subjects diagnosed with bipolar disorder or schizophrenia. *Biol Psychiatry*. 2007;62:884–93.
34. Bezchlibnyk YB, Sun X, Wang J-F, MacQueen GM, McEwen BS, Young LT. Neuron somal size is decreased in the lateral amygdalar nucleus of subjects with bipolar disorder. *J Psychiatry Neurosci*. 2007;32:203–10.
35. Bielau H, Trübner K, Krell D, Agelink MW, Bernstein HG, Stauch R, et al. Volume deficits of subcortical nuclei in mood disorders. *Eur Arch Psychiatry Clin Neurosci*. 2005;255:401–12.
36. Bouras C, Kövari E, Hof PR, Riederer BM, Giannakopoulos P. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. *Acta Neuropathol*. 2001;102:373–9.
37. Toker L, Mancarci BO, Tripathy S, Pavlidis P. Transcriptomic evidence for alterations in astrocytes and parvalbumin interneurons in subjects with bipolar disorder and schizophrenia. *Biol Psychiatry*. 2018;84:787–96.
38. Wang AY, Lohmann KM, Yang CK, Zimmerman EI, Pantazopoulos H, Herring N, et al. Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. *Acta Neuropathol*. 2011;122:615–26.
39. Krüger S, Alda M, Young LT, Goldapple K, Parikh S, Mayberg HS. Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. *Am J Psychiatry*. 2006;163:257–64.
40. Urback AL, Metcalfe AW, Korczak DJ, MacIntosh BJ, Goldstein BI. Reduced cerebrovascular reactivity among adolescents with bipolar disorder. *Bipolar Disord*. 2019;21:124–31.
41. Toma S, MacIntosh BJ, Swardfager W, Goldstein BI. Cerebral blood flow in bipolar disorder: a systematic review. *J Affect Disord*. 2018;241:505–13.
42. Zeng V, Lizano P, Bolo NR, Lutz O, Brady R Jr, Ivleva EI, et al. Altered cerebral perfusion in bipolar disorder: a pCASL MRI study. *Bipolar Disord*. 2021;23:130–40.
43. Oh DH, Son H, Hwang S, Kim SH. Neuropathological abnormalities of astrocytes, GABAergic neurons, and pyramidal neurons in the dorsolateral prefrontal cortices of patients with major depressive disorder. *Eur Neuropsychopharmacol*. 2012;22:330–8.
44. Chandley MJ, Szebeni K, Szebeni A, Crawford J, Stockmeier CA, Turecki G, et al. Gene expression deficits in pontine locus coeruleus astrocytes in men with major depressive disorder. *J Psychiatry Neurosci*. 2013;38:276–84.
45. Aston C, Jiang L, Sokolov B. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Mol Psychiatry*. 2005;10:309–22.
46. Rajkowska G, Mahajan G, Maciag D, Sathyanesan M, Iyo AH, Moulana M, et al. Oligodendrocyte morphometry and expression of myelin-related mRNA in ventral prefrontal white matter in major depressive disorder. *J Psychiatr Res*. 2015;65:53–62.

47. Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry*. 2001;58:545–53.
48. Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry*. 2000;48:766–77.
49. Boldrini M, Galvaly H, Dwork AJ, Rosoklija GB, Trencavska-Ivanovska I, Pavlovski G, et al. Resilience is associated with larger dentate gyrus, while suicide decedents with major depressive disorder have fewer granule neurons. *Biol Psychiatry*. 2019;85:850–62.
50. Darling AM, Richey RE, Akins JD, Saunders EF, Brothers RM, Greaney JL. Cerebrovascular reactivity is blunted in young adults with major depressive disorder: The influence of current depressive symptomology. *J Affect Disord*. 2021;295:513–21.
51. de Castro AG-C, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P. Cerebrovascular reactivity in depressed patients without vascular risk factors. *J Psychiatr Res*. 2008;42:78–82.
52. Kaichi Y, Okada G, Takamura M, Toki S, Akiyama Y, Higaki T, et al. Changes in the regional cerebral blood flow detected by arterial spin labeling after 6-week escitalopram treatment for major depressive disorder. *J Affect Disord*. 2016;194:135–43.
53. Massardo T, Quintana JC, Jaimovich R, Sáez CG, Risco L, Liberman C, et al. Regional brain perfusion is associated with endothelial dysfunction markers in major depressive disorder. *Neuropsychobiology*. 2021;80:214–24.
54. Ota M, Noda T, Sato N, Hattori K, Teraishi T, Hori H, et al. Characteristic distributions of regional cerebral blood flow changes in major depressive disorder patients: a pseudo-continuous arterial spin labeling (pCASL) study. *J Affect Disord*. 2014;165:59–63.
55. Notter T. Astrocytes in schizophrenia. *Brain Neurosci Adv*. 2021;5:23982128211009148.
56. Trépanier M, Hopperton K, Mizrahi R, Mechawar N, Bazinet R. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Mol Psychiatry*. 2016;21:1009–26.
57. Williams MR, Hampton T, Pearce RK, Hirsch SR, Ansorge O, Thom M, et al. Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2013;263:41–52.
58. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res*. 2004;67:269–75.
59. Hof PR, Haroutunian V, Friedrich VL, Byne W, Buitron C. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. *Biol psychiatry*. 2009;53:1075–85.
60. Stone WS, Phillips MR, Yang LH, Kegeles LS, Susser ES, Lieberman JA. Neurodegenerative model of schizophrenia: growing evidence to support a revisit. *Schizophr Res*. 2022;243:154–62.
61. Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. *Biol Psychiatry*. 2002;52:708–15.
62. Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry*. 1998;44:88–97.
63. Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry*. 1999;45:395–402.
64. Casas BS, Vitória G, Prieto CP, Casas M, Chacón C, Uhrig M, et al. Schizophrenia-derived hiPSC brain microvascular endothelial-like cells show impairments in angiogenesis and blood–brain barrier function. *Mol Psychiatry*. 2022. <https://doi.org/10.1038/s41380-022-01653-0>.
65. De Picker LJ, Morrens M, Chance SA, Boche D. Microglia and brain plasticity in acute psychosis and schizophrenia illness course: a meta-review. *Front Psych*. 2017;8:238.
66. Ekonomou A, Savva G, Brayne C, Forster G, Francis P, Johnson M, Medical Research Council Cognitive Function and Ageing Neuropathology Study, et al. Stage-specific changes in neurogenic and glial markers in Alzheimer's disease. *Biol Psychiatry*. 2015;77:711–9.
67. Marina N, Christie IN, Korsak A, Doronin M, Brazhe A, Hosford PS, et al. Astrocytes monitor cerebral perfusion and control systemic circulation to maintain brain blood flow. *Nat Commun*. 2020;11:1–9.
68. Kapogiannis D, Mattson MP. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurol*. 2011;10:187–98.
69. Roth AD, Ramírez G, Alarcón R, Von Bernhardi R. Oligodendrocytes damage in Alzheimer's disease: beta amyloid toxicity and inflammation. *Biol Res*. 2005;38:381–7.
70. Leng K, Li E, Eser R, Piergies A, Sit R, Tan M, et al. Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. *Nat Neurosci*. 2021;24:276–87.
71. Pimentel-Coelho PM, Rivest S. The early contribution of cerebrovascular factors to the pathogenesis of Alzheimer's disease. *Eur J Neurosci*. 2012;35:1917–37.
72. Park L, Wang G, Zhou P, Zhou J, Pitstick R, Previti ML, et al. Scavenger receptor CD36 is essential for the cerebrovascular oxidative stress and neurovascular dysfunction induced by amyloid- β . *Proc Natl Acad Sci*. 2011;108:5063–8.
73. Brundel M, De Bresser J, Van Dillen JJ, Kappelle LJ, Biessels GJ. Cerebral microinfarcts: a systematic review of neuropathological studies. *J Cereb Blood Flow Metab*. 2012;32:425–36.
74. Gill T, Watling SE, Richardson JD, McCluskey T, Tong J, Meyer JH, et al. Imaging of astrocytes in posttraumatic stress disorder: a PET study with the monoamine oxidase B radioligand [^{11}C] SL25.1188. *Eur Neuropsychopharmacol*. 2022;54:54–61.
75. Tynan RJ, Beynon SB, Hinwood M, Johnson SJ, Nilsson M, Woods JJ, et al. Chronic stress-induced disruption of the astrocyte network is driven by structural atrophy and not loss of astrocytes. *Acta Neuropathol*. 2013;126:75–91.
76. Logue MW, Zhou Z, Morrison FG, Wolf EJ, Daskalakis NP, Chatzinakos C, et al. Gene expression in the dorsolateral and ventromedial prefrontal cortices implicates immune-related gene networks in PTSD. *J Clin Psychopharmacol*. 2021;15: 100398.
77. Bonnefil V, Dietz K, Amatruda M, Wentling M, Aubry AV, Dupree JL, et al. Region-specific myelin differences define behavioral consequences of chronic social defeat stress in mice. *Elife*. 2019;8: e40855.
78. Liu J, Dietz K, Hodes GE, Russo SJ, Casaccia P. Widespread transcriptional alternations in oligodendrocytes in the adult mouse brain following chronic stress. *Dev Neurobiol*. 2018;78:152–62.
79. Lotocki G, de Rivero VJ, Alonso O, Molano JS, Nixon R, Safavi P, et al. Oligodendrocyte vulnerability following traumatic brain injury in rats. *Neurosci Lett*. 2011;499:143–8.
80. Smith KL, Kassem MS, Clarke DJ, Kuligowski MP, Bedoya-Pérez MA, Todd SM, et al. Microglial cell hyper-ramification and neuronal dendritic spine loss in the hippocampus and medial prefrontal cortex in a mouse model of PTSD. *Brain Behav Immun*. 2019;80:889–99.

81. Assis-Nascimento P, Tsenkina Y, Liebl DJ. EphB3 signaling induces cortical endothelial cell death and disrupts the blood–brain barrier after traumatic brain injury. *Cell Death Dis.* 2018. <https://doi.org/10.1038/s41419-017-0016-5>.
82. Nahum K, Todder D, Zohar J, Cohen H. The role of microglia in the (Mal) adaptive response to traumatic experience in an animal model of PTSD. *Int J Mol Sci.* 2022;23:7185.
83. Sun R, Zhang Z, Lei Y, Liu Y, Ce Lu, Rong H, et al. Hippocampal activation of microglia may underlie the shared neurobiology of comorbid posttraumatic stress disorder and chronic pain. *Mol Pain.* 2016;12:1744806916679166.
84. Wu W, Zhang X, Zhou J, Yang H, Chen J, Zhao L, et al. Clemastine ameliorates perioperative neurocognitive disorder in aged mice caused by anesthesia and surgery. *Front Pharmacol.* 2021. <https://doi.org/10.3389/fphar.2021.738590>.
85. Carlström KE, Zhu K, Ewing E, Krabbendam IE, Harris RA, Falcão AM, et al. Gsta4 controls apoptosis of differentiating adult oligodendrocytes during homeostasis and remyelination via the mitochondria-associated Fas-Casp8-Bid-axis. *Nat Commun.* 2020;11:1–13.
86. Green AJ, Gelfand JM, Cree BA, Bevan C, Boscardin WJ, Mei F, et al. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *The Lancet.* 2017;390:2481–9.
87. Li Z, He Y, Fan S, Sun B. Clemastine rescues behavioral changes and enhances remyelination in the cuprizone mouse model of demyelination. *Neurosci Bull.* 2015;31:617–25.
88. Wang F, Yang Y-J, Yang N, Chen X-J, Huang N-X, Zhang J, et al. Enhancing oligodendrocyte myelination rescues synaptic loss and improves functional recovery after chronic hypoxia. *Neuron.* 2018;99(689–701): e5.
89. Chen J-F, Liu K, Hu B, Li R-R, Xin W, Chen H, et al. Enhancing myelin renewal reverses cognitive dysfunction in a murine model of Alzheimer's disease. *Neuron.* 2021. <https://doi.org/10.1016/j.neuron.2021.05.012>.
90. Cree BA, Niu J, Hoi KK, Zhao C, Caganap SD, Henry RG, et al. Clemastine rescues myelination defects and promotes functional recovery in hypoxic brain injury. *Brain.* 2018;141:85–98.
91. Liu N, Wang W, Zhang R, Han H. Effects of clemastine fumarate on expression of toll like receptor 4 in lung ischemia-reperfusion. *J Pract Med.* 2016;32:2988–91.
92. Alberdi E, Sánchez-Gómez MV, Matute C. Calcium and glial cell death. *J Clin Psychopharmacol.* 2005;38:417–25.
93. Su W-J, Zhang T, Jiang C-L, Wang W. Clemastine alleviates depressive-like behavior through reversing the imbalance of microglia-related pro-inflammatory state in mouse hippocampus. *Front Cell Neurosci.* 2018. <https://doi.org/10.3389/fncel.2018.00412>.
94. Yuan F, Wang T. Glutamate-induced swelling of cultured astrocytes is mediated by metabotropic glutamate receptor. *Sci China C Life Sci.* 1996;39:517–22.
95. Salinska E, Sobczuk A, Lazarewicz JW. Dantrolene antagonizes the glycineB site of the NMDA receptor. *Neurosci Lett.* 2008;432:137–40.
96. Lei SZ, Zhang D, Abele AE, Lipton SA. Blockade of NMDA receptor-mediated mobilization of intracellular Ca²⁺ prevents neurotoxicity. *Brain Res.* 1992;598:196–202.
97. Kelliher M, Fastbom J, Cowburn R, Bonkale W, Ohm T, Ravid R, et al. Alterations in the ryanodine receptor calcium release channel correlate with Alzheimer's disease neurofibrillary and β -amyloid pathologies. *Neuroscience.* 1999;92:499–513.
98. Chakroborty S, Goussakov I, Miller MB, Stutzmann GE. Deviant ryanodine receptor-mediated calcium release resets synaptic homeostasis in presymptomatic 3xTg-AD mice. *J Neurosci.* 2009;29:9458–70.
99. Muehlschlegel S, Sims JR. Dantrolene: mechanisms of neuroprotection and possible clinical applications in the neurointensive care unit. *Neurocrit Care.* 2009;10:103–15.
100. Liou B, Peng Y, Li R, Inskeep V, Zhang W, Quinn B, et al. Modulating ryanodine receptors with dantrolene attenuates neuronopathic phenotype in Gaucher disease mice. *Hum Mol Genet.* 2016;25:5126–41.
101. Keles I, Bozkurt MF, Aglamis E, Fidan AF, Ceylan C, Karalar M, et al. Protective effects of dantrolene and methylprednisolone against spinal cord injury-induced early oxidative damage in rabbit bladder: a comparative experimental study. *Adv Clin Exp Med.* 2019. <https://doi.org/10.17219/acem/110326>.
102. Todorova VK, Siegel ER, Kaufmann Y, Kumarapeli A, Owen A, Wei JY, et al. Dantrolene attenuates cardiotoxicity of doxorubicin without reducing its antitumor efficacy in a breast cancer model. *Transl Oncol.* 2020;13:471–80.
103. Zhang L, Andou Y, Masuda S, Mitani A, Kataoka K. Dantrolene protects against ischemic, delayed neuronal death in gerbil brain. *Neurosci Lett.* 1993;158:105–8.
104. Rowley HL, Marsden CA, Martin KF. Generalised seizure-induced changes in rat hippocampal glutamate but not GABA release are potentiated by repeated seizures. *Neurosci Lett.* 1997;234:143–6.
105. Gursoy ID, Barun S, Erdem R, Keskin U, Kiziltas M, Atilla P, et al. Investigation of the possible protective effects of ketamine and dantrolene on the hippocampal apoptosis and spatial learning in rats exposed to repeated electroconvulsive seizures as a model of status epilepticus. *Turk Neurosurg.* 2020. <https://doi.org/10.5137/1019-5149.JTN.27023-19.3>.
106. Chen X, Wu J, Lvovskaya S, Herndon E, Supnet C, Bezprozvanny I. Dantrolene is neuroprotective in Huntington's disease transgenic mouse model. *Mol Neurodegener.* 2011;6:1–12.
107. Wang H, Ward N, Boswell M, Katz DM. Secretion of brain-derived neurotrophic factor from brain microvascular endothelial cells. *Eur J Neurosci.* 2006;23:1665–70.
108. Sugawa M, Sakurai Y, Ishikawa-Ieda Y, Suzuki H, Asou H. Effects of erythropoietin on glial cell development; oligodendrocyte maturation and astrocyte proliferation. *Neurosci Res.* 2002;4:391–403.
109. Wakhloo D, Scharkowski F, Curto Y, Butt UJ, Bansal V, Steixner-Kumar AA, et al. Functional hypoxia drives neuroplasticity and neurogenesis via brain erythropoietin. *Nat Commun.* 2020;11:1–12.
110. Viviani B, Bartesaghi S, Corsini E, Villa P, Ghezzi P, Garau A, et al. Erythropoietin protects primary hippocampal neurons increasing the expression of brain-derived neurotrophic factor. *J Neurochem.* 2005;93:412–21.
111. Osredkar D, Sall JW, Bickler PE, Ferriero DM. Erythropoietin promotes hippocampal neurogenesis in in vitro models of neonatal stroke. *Neurobiol Dis.* 2010;38:259–65.
112. Adamcio B, Sargin D, Stradomska A, Medrihan L, Gertler C, Theis F, et al. Erythropoietin enhances hippocampal long-term potentiation and memory. *BMC Biol.* 2008;6:37.
113. Tazangi PE, Moosavi SMS, Shabani M, Haghani M. Erythropoietin improves synaptic plasticity and memory deficits by decrease of the neurotransmitter release probability in the rat model of Alzheimer's disease. *Pharmacol Biochem Behav.* 2015;130:15–21.

114. Weber A, Maier RF, Hoffmann U, Grips M, Hoppenz M, Aktas AG, et al. Erythropoietin improves synaptic transmission during and following ischemia in rat hippocampal slice cultures. *Brain Res.* 2002;958:305–11.
115. Xiong Y, Chopp M, Lee C-P. Erythropoietin improves brain mitochondrial function in rats after traumatic brain injury. *Neurol Res.* 2009;31:496–502.
116. Chong ZZ, Kang J-Q, Maiese K. Erythropoietin is a novel vascular protectant through activation of Akt1 and mitochondrial modulation of cysteine proteases. *Circulation.* 2002;106:2973–9.
117. Tamura T, Aoyama M, Ukai S, Kakita H, Sobue K, Asai K. Neuroprotective erythropoietin attenuates microglial activation, including morphological changes, phagocytosis, and cytokine production. *Brain Res.* 2017;1662:65–74.
118. Choi JW, Gardell SE, Herr DR, Rivera R, Lee C-W, Noguchi K, et al. FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc Natl Acad Sci.* 2011;108:751–6.
119. Hoffmann FS, Hofreiter J, Rübsamen H, Melms J, Schwarz S, Faber H, et al. Fingolimod induces neuroprotective factors in human astrocytes. *J Neuroinflammation.* 2015;12:1–13.
120. van Doorn R, Nijland PG, Dekker N, Witte ME, Lopes-Pinheiro MA, van het Hof B, et al. Fingolimod attenuates ceramide-induced blood–brain barrier dysfunction in multiple sclerosis by targeting reactive astrocytes. *Acta Neuropathol.* 2012;124:397–410.
121. Spiegel S, Milstien S. Sphingosine-1-phosphate: signaling inside and out. *FEBS Lett.* 2000;476:55–7.
122. Cruz VT, Fonseca J. Central effects of fingolimod. *Rev Neurol.* 2014;59:121–8.
123. Zhang J, Zhang Z, Li Y, Ding X, Shang X, Lu M, et al. Fingolimod treatment promotes proliferation and differentiation of oligodendrocyte progenitor cells in mice with experimental autoimmune encephalomyelitis. *Neurobiol Dis.* 2015;76:57–66.
124. Yasuda K, Maki T, Saito S, Yamamoto Y, Kinoshita H, Choi YK, et al. Effect of fingolimod on oligodendrocyte maturation under prolonged cerebral hypoperfusion. *Brain Res.* 2019;1720: 146294.
125. Yin P, Xue Y, Wang T, Zhong D, Li G. The therapeutic targets of fingolimod (FTY720) are involved in pathological processes in the frontal cortex of Alzheimer's disease patients: a network pharmacology study. *Front Aging Neurosci.* 2021;13:6.
126. Joshi P, Gabrielli M, Ponzoni L, Pelucchi S, Stravalaci M, Beeg M, et al. Fingolimod limits acute A β neurotoxicity and promotes synaptic versus extrasynaptic NMDA receptor functionality in hippocampal neurons. *Sci Rep.* 2017;7:1–15.
127. Miron VE, Ludwin SK, Darlington PJ, Jarjour AA, Soliven B, Kennedy TE, et al. Fingolimod (FTY720) enhances remyelination following demyelination of organotypic cerebellar slices. *Am J Pathol.* 2010;176:2682–94.
128. Di Menna L, Molinaro G, Di Nuzzo L, Rizzo B, Zappulla C, Pozzilli C, et al. Fingolimod protects cultured cortical neurons against excitotoxic death. *Pharmacol Res.* 2013;67:1–9.
129. Gurevich M, Waknin R, Stone E, Achiron A. Fingolimod-improved axonal and myelin integrity of white matter tracts associated with multiple sclerosis-related functional impairments. *CNS Neurosci Ther.* 2018;24:412–9.
130. Gol M, Ghorbanian D, Hassanzadeh S, Javan M, Mirnajafi-Zadeh J, Ghasemi-Kasman M. Fingolimod enhances myelin repair of hippocampus in pentylentetrazol-induced kindling model. *Eur J Pharm Sci.* 2017;96:72–83.
131. Patnaik A, Spiombi E, Frasca A, Landsberger N, Zagrebelsky M, Korte M. Fingolimod modulates dendritic architecture in a BDNF-dependent manner. *Int J Mol Sci.* 2020;21:3079.
132. Rossi S, Lo Giudice T, De Chiara V, Musella A, Studer V, Motta C, et al. Oral fingolimod rescues the functional deficits of synapses in experimental autoimmune encephalomyelitis. *Br J Pharmacol.* 2012;165:861–9.
133. Candadai AA, Liu F, Verma A, Adil MS, Alfarhan M, Fagan SC, et al. Neuroprotective effects of fingolimod in a cellular model of optic neuritis. *Cells.* 2021;10:2938.
134. Bai B, Lunn S, Avila R, Wang J, Chmura D, Benson E, Kidd G, Medicetty S, Trapp B. Fingolimod reduces axonal transection during demyelination (P1. 153). *AAN Enterprises*; 2015.
135. Noda H, Takeuchi H, Mizuno T, Suzumura A. Fingolimod phosphate promotes the neuroprotective effects of microglia. *J Neuroimmunol.* 2013;256:13–8.
136. Qin C, Fan W-H, Liu Q, Shang K, Murugan M, Wu L-J, et al. Fingolimod protects against ischemic white matter damage by modulating microglia toward M2 polarization via STAT3 pathway. *Stroke.* 2017;48:3336–46.
137. Kinoshita M, Hirayama Y, Fujishita K, Shibata K, Shinozaki Y, Shigetomi E, et al. Anti-depressant fluoxetine reveals its therapeutic effect via astrocytes. *EBioMedicine.* 2018;32:72–83.
138. Czéh B, Müller-Keuker JI, Rygula R, Abumaria N, Hiemke C, Domenici E, et al. Chronic social stress inhibits cell proliferation in the adult medial prefrontal cortex: hemispheric asymmetry and reversal by fluoxetine treatment. *Neuropsychopharmacology.* 2007;32:1490–503.
139. de Leeuw VC, Hessel EV, Pennings JL, Hodemaekers HM, Wackers PF, van Oostrom CT, et al. Differential effects of fluoxetine and venlafaxine in the neural embryonic stem cell test (ESTn) revealed by a cell lineage map. *Neurotoxicology.* 2020;76:1–9.
140. Lee JY, Kang SR, Yune TY. Fluoxetine prevents oligodendrocyte cell death by inhibiting microglia activation after spinal cord injury. *J Neurotrauma.* 2015;32:633–44.
141. Ofek K, Schoknecht K, Melamed-Book N, Heinemann U, Friedman A, Soreq H. Fluoxetine induces vasodilatation of cerebral arterioles by co-modulating NO/muscarinic signalling. *J Cell Mol Med.* 2012;16:2736–44.
142. Chung YC, Kim SR, Park J-Y, Chung ES, Park KW, Won SY, et al. Fluoxetine prevents MPTP-induced loss of dopaminergic neurons by inhibiting microglial activation. *Neuropharmacology.* 2011;60:963–74.
143. Lee JY, Lee HE, Kang SR, Choi HY, Ryu JH, Yune TY. Fluoxetine inhibits transient global ischemia-induced hippocampal neuronal death and memory impairment by preventing blood–brain barrier disruption. *Neuropharmacology.* 2014;79:161–71.
144. Allaman I, Fiumelli H, Magistretti PJ, Martin J-L. Fluoxetine regulates the expression of neurotrophic/growth factors and glucose metabolism in astrocytes. *Psychopharmacology.* 2011;216:75–84.
145. Mercier G, Lennon AM, Renouf B, Dessouroux A, Ramaugé M, Courtin F, et al. MAP kinase activation by fluoxetine and its relation to gene expression in cultured rat astrocytes. *J Mol Neurosci.* 2004;24:207–16.
146. Shu X, Sun Y, Sun X, Zhou Y, Bian Y, Shu Z, et al. The effect of fluoxetine on astrocyte autophagy flux and injured mitochondria clearance in a mouse model of depression. *Cell Death Dis.* 2019;10:1–16.
147. Chao F-I, Zhang Y, Zhang L, Jiang L, Zhou C-n, Tang J, et al. Fluoxetine promotes hippocampal oligodendrocyte maturation and delays learning and memory decline in APP/PS1 mice. *Front Aging Neurosci.* 2021. <https://doi.org/10.3389/fnagi.2020.627362>.

148. Bianchi M, Shah AJ, Fone KC, Atkins AR, Dawson LA, Heidebreder CA, et al. Fluoxetine administration modulates the cytoskeletal microtubular system in the rat hippocampus. *Synapse*. 2009;63:359–64.
149. Stanisavljević A, Perić I, Gass P, Inta D, Lang UE, Borgwardt S, et al. Fluoxetine modulates neuronal activity in stress-related limbic areas of adult rats subjected to the chronic social isolation. *Brain Res Bull*. 2020;163:95–108.
150. Ma J, Gao Y, Jiang L, Chao F-I, Huang W, Zhou C-n, et al. Fluoxetine attenuates the impairment of spatial learning ability and prevents neuron loss in middle-aged APP^{swe}/PSEN1^{dE9} double transgenic Alzheimer's disease mice. *Oncotarget*. 2017;8:27676.
151. Dhimi K, Churchward M, Baker G, Todd K. Fluoxetine and citalopram decrease microglial release of glutamate and D-serine to promote cortical neuronal viability following ischemic insult. *Mol Cell Neurosci*. 2013;56:365–74.
152. Hu Q, Liu L, Zhou L, Lu H, Wang J, Chen X, et al. Effect of fluoxetine on HIF-1 α -Netrin/VEGF cascade, angiogenesis and neuroprotection in a rat model of transient middle cerebral artery occlusion. *Exp Neurol*. 2020;329: 113312.
153. Zhang F, Zhou H, Wilson BC, Shi J-S, Hong J-S, Gao H-M. Fluoxetine protects neurons against microglial activation-mediated neurotoxicity. *Parkinsonism Relat Disord*. 2012;18:S213–7.
154. Rivera AD, Butt AM. Astrocytes are direct cellular targets of lithium treatment: novel roles for lysyl oxidase and peroxisome-proliferator activated receptor- γ as astroglial targets of lithium. *Transl Psychiatry*. 2019;9:1–14.
155. Kim HJ, Thayer SA. Lithium increases synapse formation between hippocampal neurons by depleting phosphoinositides. *Mol Pharmacol*. 2009;75:1021–30.
156. Green MV, Pengo T, Raybuck JD, Naqvi T, McMullan HM, Hawkinson JE, et al. Automated live-cell imaging of synapses in rat and human neuronal cultures. *Front Cell Neurosci*. 2019;13:467.
157. Kerr F, Bjedov I, Sofola-Adesakin O. Molecular mechanisms of lithium action: switching the light on multiple targets for dementia using animal models. *Front Mol Neurosci*. 2018. <https://doi.org/10.3389/fnmol.2018.00297>.
158. Voytovych H, Krivánková L, Ziemann U. Lithium: a switch from LTD-to LTP-like plasticity in human cortex. *Neuropharmacology*. 2012;63:274–9.
159. Son H, Yu IT, Hwang SJ, Kim JS, Lee SH, Lee YS, et al. Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. *J Neurochem*. 2003;85:872–81.
160. Emamghoreishi M, Keshavarz M, Nekooeian AA. Acute and chronic effects of lithium on BDNF and GDNF mRNA and protein levels in rat primary neuronal, astroglial and neuroastroglia cultures. *Iran J Basic Med Sci*. 2015;18:240.
161. Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *J Neurochem*. 2000;75:1729–34.
162. Fiorentini A, Rosi MC, Grossi C, Luccarini I, Casamenti F. Lithium improves hippocampal neurogenesis, neuropathology and cognitive functions in APP mutant mice. *PLoS ONE*. 2010;5: e14382.
163. Dwivedi T, Zhang H. Lithium-induced neuroprotection is associated with epigenetic modification of specific BDNF gene promoter and altered expression of apoptotic-regulatory proteins. *Front Neurosci*. 2015;8:457.
164. Fornai F, Longone P, Cafaro L, Kastsiuchenka O, Ferrucci M, Manca ML, et al. Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci*. 2008;105:2052–7.
165. Maurer IC, Schippel P, Volz HP. Lithium-induced enhancement of mitochondrial oxidative phosphorylation in human brain tissue. *Bipolar Disord*. 2009;11:515–22.
166. Shalbuyeva N, Brustovetsky T, Brustovetsky N. Lithium Desensitizes Brain Mitochondria to Calcium, Antagonizes Permeability Transition, and Diminishes Cytochrome c Release. *J Biol Chem*. 2007;282:18057–68.
167. Guo S, Arai K, Stins MF, Chuang D-M, Lo EH. Lithium upregulates vascular endothelial growth factor in brain endothelial cells and astrocytes. *Stroke*. 2009;40:652–5.
168. Ji Y-B, Gao Q, Tan X-X, Huang X-W, Ma Y-Z, Fang C, et al. Lithium alleviates blood-brain barrier breakdown after cerebral ischemia and reperfusion by upregulating endothelial Wnt/ β -catenin signaling in mice. *Neuropharmacology*. 2021;186: 108474.
169. Nassar A, Azab AN. Effects of lithium on inflammation. *ACS Chem Neurosci*. 2014;5:451–8.
170. Dong H, Zhang X, Dai X, Lu S, Gui B, Jin W, et al. Lithium ameliorates lipopolysaccharide-induced microglial activation via inhibition of toll-like receptor 4 expression by activating the PI3K/Akt/FoxO1 pathway. *J Neuroinflammation*. 2014;11:140.
171. Li N, Zhang X, Dong H, Zhang S, Sun J, Qian Y. Lithium ameliorates LPS-induced astrocytes activation partly via inhibition of toll-like receptor 4 expression. *Cell Physiol Biochem*. 2016;38:714–25.
172. Torrez VR, Zimmer ER, Kalinine E, Haas CB, Zenki KC, Muller AP, et al. Memantine mediates astrocytic activity in response to excitotoxicity induced by PP2A inhibition. *Neurosci Lett*. 2019;696:179–83.
173. Ma G, Liu C, Hashim J, Conley G, Morriss N, Meehan WP, et al. Memantine mitigates oligodendrocyte damage after repetitive mild traumatic brain injury. *Neuroscience*. 2019;421:152–61.
174. Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. *Neurochem*. 2006;97:1611–26.
175. Dimpfel W. Effects of memantine on synaptic transmission in the hippocampus in vitro. *Arzneimittelforschung*. 1995;45:1–5.
176. Volbracht C, Van Beek J, Zhu C, Blomgren K, Leist M. Neuroprotective properties of memantine in different in vitro and in vivo models of excitotoxicity. *Eur J Neurosci*. 2006;23:2611–22.
177. Liu Y, Huang Y, Xu Y, Qu P, Wang M. Memantine protects against ischemia/reperfusion-induced brain endothelial permeability. *IUBMB Life*. 2018;70:336–43.
178. Davies VJ, Hollins AJ, Piechota MJ, Yip W, Davies JR, White KE, et al. Opa1 deficiency in a mouse model of autosomal dominant optic atrophy impairs mitochondrial morphology, optic nerve structure and visual function. *Hum Mol Genet*. 2007;16:1307–18.
179. Kushnareva Y, Gerencser A, Bossy B, Ju W, White A, Waggoner J, et al. Loss of OPA1 disturbs cellular calcium homeostasis and sensitizes for excitotoxicity. *Cell Death Differ*. 2013;20:353–65.
180. Ju W-K, Kim K-Y, Angert M, Duong-Polk KX, Lindsey JD, Ellisman MH, et al. Memantine blocks mitochondrial OPA1 and cytochrome c release and subsequent apoptotic cell death in glaucomatous retina. *Invest Ophthalmol Vis Sci*. 2009;50:707–16.
181. McAllister J, Ghosh S, Berry D, Park M, Sadeghi S, Wang KX, et al. Effects of memantine on mitochondrial function. *Biochem Pharmacol*. 2008;75:956–64.

182. Maskell PD, Speder P, Newberry NR, Bermudez I. Inhibition of human $\alpha 7$ nicotinic acetylcholine receptors by open channel blockers of N-methyl-D-aspartate receptors. *Br J Pharmacol*. 2003;140:1313–9.
183. Wang F, Zou Z, Gong Y, Yuan D, Chen X, Sun T. Regulation of human brain microvascular endothelial cell adhesion and barrier functions by memantine. *J Mol Neurosci*. 2017;62:123–9.
184. Schmitz T, Endesfelder S, Chew LJ, Zaak I, Bühner C. Minocycline protects oligodendroglial precursor cells against injury caused by oxygen-glucose deprivation. *J Neurosci Res*. 2012;90:933–44.
185. Yune TY, Lee JY, Jung GY, Kim SJ, Jiang MH, Kim YC, et al. Minocycline alleviates death of oligodendrocytes by inhibiting pro-nerve growth factor production in microglia after spinal cord injury. *J Neurosci*. 2007;27:7751–61.
186. Zhao Y, Xiao M, He W, Cai Z. Minocycline upregulates cyclic AMP response element binding protein and brain-derived neurotrophic factor in the hippocampus of cerebral ischemia rats and improves behavioral deficits. *Neuropsychiatr Dis Treat*. 2015;11:507.
187. Burgos-Ramos E, Puebla-Jiménez L, Arilla-Ferreiro E. Minocycline provides protection against β -amyloid (25–35)-induced alterations of the somatostatin signaling pathway in the rat temporal cortex. *Neuroscience*. 2008;154:1458–66.
188. Jiang Y, Liu Y, Zhu C, Ma X, Ma L, Zhou L, et al. Minocycline enhances hippocampal memory, neuroplasticity and synapse-associated proteins in aged C57 BL/6 mice. *Neurobiol Learn Mem*. 2015;121:20–9.
189. Fujita Y, Ishima T, Kunitachi S, Hagiwara H, Zhang L, Iyo M, et al. Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antibiotic drug minocycline. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:336–9.
190. Miao H, Li R, Han C, Lu X, Zhang H. Minocycline promotes posthemorrhagic neurogenesis via M2 microglia polarization via upregulation of the TrkB/BDNF pathway in rats. *J Neurophysiol*. 2018;120:1307–17.
191. Hashimoto K, Ishima T. A novel target of action of minocycline in NGF-induced neurite outgrowth in PC12 cells: translation initiation factor eIF4A1. *PLoS ONE*. 2010;5: e15430.
192. Hunter CL, Bachman D, Granholm AC. Minocycline prevents cholinergic loss in a mouse model of Down's syndrome. *Ann Neurol: Official J Am Neurol Assoc Child Neurol Soc*. 2004;56:675–88.
193. Wang X, Zhu S, Pei Z, Drozda M, Stavrovskaya IG, Del Signore SJ, et al. Inhibitors of cytochrome c release with therapeutic potential for Huntington's disease. *J Neurosci*. 2008;28:9473–85.
194. Fernandez-Gomez F, Galindo M, Gomez-Lazaro M, González-García C, Ceña V, Aguirre N, et al. Involvement of mitochondrial potential and calcium buffering capacity in minocycline cytoprotective actions. *Neuroscience*. 2005;133:959–67.
195. Yoon S-Y, Patel D, Dougherty P. Minocycline blocks lipopolysaccharide induced hyperalgesia by suppression of microglia but not astrocytes. *Neuroscience*. 2012;221:214–24.
196. Lai AY, Todd KG. Hypoxia-activated microglial mediators of neuronal survival are differentially regulated by tetracyclines. *Glia*. 2006;53:809–16.
197. Gray E, Ginty M, Kemp K, Scolding N, Wilkins A. The PPAR- γ agonist pioglitazone protects cortical neurons from inflammatory mediators via improvement in peroxisomal function. *J Neuroinflammation*. 2012. <https://doi.org/10.1186/1742-2094-9-63>.
198. Kanakasabai S, Pestereva E, Chearwae W, Gupta SK, Ansari S, Bright JJ. PPAR γ agonists promote oligodendrocyte differentiation of neural stem cells by modulating stemness and differentiation genes. *PLoS ONE*. 2012;7: e50500.
199. Huang W, Shao M, Liu H, Chen J, Hu J, Zhu L, et al. Fibroblast growth factor 21 enhances angiogenesis and wound healing of human brain microvascular endothelial cells by activating PPAR γ . *J Pharmacol Sci*. 2019;140:120–7.
200. Bernardo A, Levi G, Minghetti L. Role of the peroxisome proliferator-activated receptor- γ (PPAR- γ) and its natural ligand 15-deoxy- Δ 12, 14-prostaglandin J2 in the regulation of microglial functions. *Eur J Neurosci*. 2000;12:2215–23.
201. Pérez-Ortiz JM, Tranque P, Vaquero CF, Domingo B, Molina F, Calvo S, et al. Glitazones differentially regulate primary astrocyte and glioma cell survival: involvement of reactive oxygen species and peroxisome proliferator-activated receptor- γ . *J Biol Chem*. 2004;279:8976–85.
202. Wang Y, Zhao W, Li G, Chen J, Guan X, Chen X, et al. Neuroprotective effect and mechanism of thiazolidinedione on dopaminergic neurons in vivo and in vitro in Parkinson's disease. *PPAR Res*. 2017. <https://doi.org/10.1155/2017/4089214>.
203. Duvanel CB, Honegger P, Pershadsingh H, Feinstein D, Matthieu JM. Inhibition of glial cell proinflammatory activities by peroxisome proliferator-activated receptor gamma agonist confers partial protection during antimyelin oligodendrocyte glycoprotein demyelination in vitro. *J Neurosci Res*. 2003;71:246–55.
204. Zhang Q, Zhu W, Xu F, Dai X, Shi L, Cai W, et al. The interleukin-4/PPAR γ signaling axis promotes oligodendrocyte differentiation and remyelination after brain injury. *PLoS Biol*. 2019;17: e3000330.
205. Bernardo A, Plumitallo C, De Nuccio C, Visentin S, Minghetti L. Curcumin promotes oligodendrocyte differentiation and their protection against TNF- α through the activation of the nuclear receptor PPAR- γ . *Sci Rep*. 2021;11:1–13.
206. Smith SA, Monteith GR, Holman NA, Robinson JA, May FJ, Roberts-Thomson SJ. Effects of peroxisome proliferator-activated receptor γ ligands ciglitazone and 15-deoxy- Δ 12, 14-prostaglandin J2 on rat cultured cerebellar granule neuronal viability. *J Neurosci Res*. 2003;72:747–55.
207. Fukunaga Y, Itoh H, Doi K, Tanaka T, Yamashita J, Chun T-H, et al. Thiazolidinediones, peroxisome proliferator-activated receptor γ agonists, regulate endothelial cell growth and secretion of vasoactive peptides. *Atherosclerosis*. 2001;158:113–9.
208. Pisanu A, Lecca D, Mulas G, Wardas J, Simbula G, Spiga S, et al. Dynamic changes in pro-and anti-inflammatory cytokines in microglia after PPAR- γ agonist neuroprotective treatment in the MPTPp mouse model of progressive Parkinson's disease. *Neurobiol Dis*. 2014;71:280–91.
209. Be G, Adamek M, Pudełko A, Małecki A, Trzeciak HI. Piracetam and vinpocetine exert cytoprotective activity and prevent apoptosis of astrocytes in vitro in hypoxia and reoxygenation. *Neurotoxicology*. 2002;1:19–31.
210. Stockburger C, Miano D, Pallas T, Friedland K, Müller WE. Enhanced neuroplasticity by the metabolic enhancer piracetam associated with improved mitochondrial dynamics and altered permeability transition pore function. *Neural Plast*. 2016. <https://doi.org/10.1155/2016/8075903>.
211. He Z, Liao Y, Zheng M, Zeng F-D, Guo L-J. Piracetam improves cognitive deficits caused by chronic cerebral hypoperfusion in rats. *Cell Mol Neurobiol*. 2008;28:613–27.
212. Yang Y, Feng J, Xu F, Wang J. Piracetam inhibits ethanol (EtOH)-induced memory deficit by mediating multiple pathways. *Brain Res*. 2017;1676:83–90.
213. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. *CNS Drug Rev*. 2005;11:169–82.

214. He Z, Hu M, Zha Y-h, Li Z-c, Zhao B, Yu L-l, et al. Piracetam ameliorated oxygen and glucose deprivation-induced injury in rat cortical neurons via inhibition of oxidative Stress, excitatory amino acids release and P53/bax. *Cell Mol Neurobiol.* 2014;4:539–47.
215. Brandao F, Paula-Barbosa MM, Cadete-Leite A. Piracetam impedes hippocampal neuronal loss during withdrawal after chronic alcohol intake. *Alcohol.* 1995;12:279–88.
216. Paula-Barbosa M, Brandao F, Pinho M, Andrade J, Madeira M, Cadete-Leite A. The effects of piracetam on lipofuscin of the rat cerebellar and hippocampal neurons after long-term alcohol treatment and withdrawal: a quantitative study. *Alcohol Clin Exp Res.* 1991;15:834–8.
217. Gupta S, Verma DK, Biswas J, Raju KSR, Joshi N, Singh S. The metabolic enhancer piracetam attenuates mitochondrion-specific endonuclease G translocation and oxidative DNA fragmentation. *Free Radical Biol Med.* 2014;73:278–90.
218. Frizzo MEdS, Dall'Onder LP, Dalcin KB, Souza DO. Riluzole enhances glutamate uptake in rat astrocyte cultures. *Cell Mol Neurobiol.* 2004;24:123–8.
219. Pereira AC, Gray JD, Kogan JF, Davidson RL, Rubin TG, Okamoto M, et al. Age and Alzheimer's disease gene expression profiles reversed by the glutamate modulator riluzole. *Mol Psychiatry.* 2017;22:296.
220. Urbani A, Belluzzi O. Riluzole inhibits the persistent sodium current in mammalian CNS neurons. *Eur J Neurosci.* 2000;12:3567–74.
221. Lesuis S, Kaplick P, Lucassen P, Krugers H. Treatment with the glutamate modulator riluzole prevents early life stress-induced cognitive deficits and impairments in synaptic plasticity in APPsw/PS1dE9 mice. *Neuropharmacology.* 2019;150:175–83.
222. Katoh-Semba R, Asano T, Ueda H, Morishita R, Takeuchi IK, Inaguma Y, Kato K. Riluzole enhances expression of brain-derived neurotrophic factor with consequent proliferation of granule precursor cells in the rat hippocampus. *FASEB J.* 2002;16(10):1328–30. <https://doi.org/10.1096/fj.02-0143fj>.
223. Malgouris C, Bardot F, Daniel M, Pellis F, Rataud J, Uzan A, et al. Riluzole, a novel ant glutamate, prevents memory loss and hippocampal neuronal damage in ischemic gerbils. *J Neurosci.* 1989;9:3720–7.
224. Kalra S, Cashman N, Genge A, Arnold D. Recovery of N-acetylaspartate in corticomotor neurons of patients With ALS After Riluzole therapy. *NeuroReport.* 1998;9:1757–61.
225. Storch A, Burkhardt K, Ludolph AC, Schwarz J. Protective effects of Riluzole on dopamine neurons: involvement of oxidative stress and cellular energy metabolism. *J Neurochem.* 2000;75:2259–69.
226. Umemiya M, Berger AJ. Inhibition by riluzole of glycinergic postsynaptic currents in rat hypoglossal motoneurons. *Br J Pharmacol.* 1995;116:3227.
227. Liu B-S, Ferreira R, Lively S, Schlichter L. Microglial SK3 and SK4 currents and activation state are modulated by the neuroprotective drug, riluzole. *J Neuroimmune Pharmacol.* 2013;8:227–37.
228. Wu Q, Zhang Y, Zhang Y, Zhang W, Zhang W, Liu Y, et al. Riluzole improves functional recovery after acute spinal cord injury in rats and may be associated with changes in spinal microglia/macrophages polarization. *Neurosci Lett.* 2020;723: 134829.
229. Lutz MW, Sprague D, Barrera J, Chiba-Falek O. Shared genetic etiology underlying Alzheimer's disease and major depressive disorder. *Transl Psychiatry.* 2020;10:1–14.
230. Duncan LE, Ratanatharathorn A, Aiello AE, Almlil LM, Amstadter AB, Ashley-Koch AE, et al. Largest GWAS of PTSD (N= 20 070) yields genetic overlap with schizophrenia and sex differences in heritability. *Mol Psychiatry.* 2018;23:666–73.
231. Consortium C-DGotPG. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet.* 2013;381:1371–9.
232. Blanchard JW, Akay LA, Davila-Velderrain J, von Maydell D, Mathys H, Davidson SM, et al. APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes. *Nature.* 2022. <https://doi.org/10.1038/s41586-022-05439-w>.
233. Lin Y-T, Seo J, Gao F, Feldman HM, Wen H-L, Penney J, et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron.* 2018;98(1141–54): e7.
234. Victor MB, Leary N, Luna X, Meharena HS, Scannail AN, Bozzelli PL, et al. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. *Cell Stem Cell.* 2022;29(1197–212): e8.
235. Rieker C, Migliavacca E, Vaucher A, Mayer FC, Baud G, Marquis J, et al. Apolipoprotein E4 expression causes gain of toxic function in isogenic human induced pluripotent stem cell-derived endothelial cells. *Arterioscler Thromb Vasc Biol.* 2019;39:e195–207.
236. Wang C, Xiong M, Gratuze M, Bao X, Shi Y, Andhey PS, et al. Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia. *Neuron.* 2021;109(1657–74): e7.
237. Brandom B, Larach M. The North American Malignant Hyperthermia Registry. Reassessment of the safety and efficacy of Dantrolene. *Anaesthesiology.* 2002;96:A1199.
238. Hemani S, Lane O, Agarwal S, Yu SP, Woodbury A. Systematic review of erythropoietin (EPO) for neuroprotection in human studies. *Neurochem Res.* 2021. <https://doi.org/10.1007/s11064-021-03242-z>.
239. Kappos L, Cohen J, Collins W, de Vera A, Zhang-Auberson L, Ritter S, et al. Fingolimod in relapsing multiple sclerosis: an integrated analysis of safety findings. *Mult Scler Related Disord.* 2014;3:494–504.
240. Beasley CM Jr, Koke SC, Nilsson ME, Gonzales JS. Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: an updated meta-analysis. *Clin Ther.* 2000;22:1319–30.
241. Messiha F. Fluoxetine: adverse effects and drug-drug interactions. *J Toxicol Clin Toxicol.* 1993;31:603–30.
242. Grandjean EM, Aubry J-M. Lithium: updated human knowledge using an evidence-based approach. *CNS Drugs.* 2009;23:397–418.
243. Schoot TS, Molmans TH, Grootens KP, Kerckhoffs AP. Systematic review and practical guideline for the prevention and management of the renal side effects of lithium therapy. *Eur Neuropsychopharmacol.* 2020;31:16–32.
244. Jiang J, Jiang H. Efficacy and adverse effects of memantine treatment for Alzheimer's disease from randomized controlled trials. *Neurol Sci.* 2015;36:1633–41.
245. Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline: report of 13 patients and review of the literature. *Arch Dermatol.* 1996;132:934–9.
246. De Reuck J, Van Vlymen B. The clinical safety of high-dose piracetam-its use in the treatment of acute stroke. *Pharmacopsychiatry.* 1999;32:33–7.
247. Liu J, Wang L-N. The efficacy and safety of riluzole for neurodegenerative movement disorders: a systematic review with meta-analysis. *Drug Deliv.* 2018;25:43–8.

248. Lee J, Green MF, Nuechterlein KH, Swerdlow NR, Greenwood TA, Helleman GS, et al. The effects of age and sex on cognitive impairment in schizophrenia: findings from the Consortium on the Genetics of Schizophrenia (COGS) study. *PLoS ONE*. 2020;15: e0232855.
249. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301:805–9.
250. Moda-Sava R, Murdock M, Parekh P, Fetcho R, Huang B, Huynh T, et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*. 2019;364: eaat8078.
251. Banasr M, Duman RS. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biol Psychiatry*. 2008;64:863–70.
252. Tasic B, Yao Z, Graybiel LT, Smith KA, Nguyen TN, Bertagnoli D, et al. Shared and distinct transcriptomic cell types across neocortical areas. *Nature*. 2018;563:72–8.
253. Bikoff JB, Gabitto MI, Rivard AF, Drobac E, Machado TA, Miri A, et al. Spinal inhibitory interneuron diversity delineates variant motor microcircuits. *Cell*. 2016;165:207–19.
254. Olislagers M, Rademaker K, Adan R, Lin B, Luykx J. Comprehensive analyses of RNA-seq and genome-wide data point to enrichment of neuronal cell type subsets in neuropsychiatric disorders. *Mol Psychiatry*. 2022;27:947–55.
255. Ståhlberg A, Andersson D, Aurelius J, Faiz M, Pekna M, Kubista M, et al. Defining cell populations with single-cell gene expression profiling: correlations and identification of astrocyte subpopulations. *Nucleic Acids Res*. 2011;39: e24.
256. Tatsumi K, Isonishi A, Yamasaki M, Kawabe Y, Morita-Takemura S, Nakahara K, et al. Olig2-lineage astrocytes: a distinct subtype of astrocytes that differs from GFAP astrocytes. *Front Neuroanat*. 2018;12:8.
257. Gandal MJ, Haney JR, Wamsley B, Yap CX, Parhami S, Emani PS, et al. Broad transcriptomic dysregulation occurs across the cerebral cortex in ASD. *Nature*. 2022;611:532–9.

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