Astrocytes and neuropsychiatric symptoms in neurodegenerative diseases: Exploring the missing links

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Abstract

Neurodegenerative diseases (ND) are characterized by primary symptoms such as cognitive or motor deficits. In addition, the presence of neuropsychiatric symptoms (NPS) in ND patients is being increasingly acknowledged as an important disease feature. Yet, their neurobiological basis remains unclear and mostly centered on neurons while overlooking astrocytes, which are crucial regulators of neuronal function underlying complex behaviors. In this opinion article, we briefly review evidence for NPS in ND and discuss their experimental assessment in preclinical models. We then present recent studies showing that astrocyte-specific dysfunctions can lead to NPS. Because many astrocyte alterations are also observed in ND, we suggest that they might underlie ND-associated NPS. We argue that there is a need for dedicated preclinical studies assessing astrocyte-based therapeutic strategies targeting NPS in the context of ND.

Highlights:

- Neuropsychiatric symptoms (NPS) are common features of neurodegenerative diseases
- NPS are often well replicated in animal models of neurodegenerative diseases
- Astrocytes are crucial regulators of neuronal function
- Astrocyte-specific dysfunctions can induce NPS
- The role of astrocytes in neurodegenerative disease-associated NPS is overlooked

Keywords

Neuron-astrocyte interactions; depressive-like symptoms; cell-specific targeting; neuronal networks; animal models; behavioral tests

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Introduction

Neurodegenerative disease (ND) main feature is the progressive dysfunction, followed by irreversible loss of neurons in specific brain regions, which determines the nature of each ND's cardinal symptoms. ND primarily affecting the brain include Alzheimer's disease (AD) and other tauopathies, which are mainly characterized by cognitive symptoms, whereas Parkinson's (PD) and Huntington's diseases (HD) classically lead to motor symptoms. In all these diseases, patients also often show neuropsychiatric symptoms (NPS). These deficits are mostly neglected as compared to "typical" cognitive or motor symptoms in ND despite their negative impact on both patient's quality of life and disease progression [1–3]. Dedicated preclinical studies to uncover the neurobiological basis of NPS in ND are sparse. Moreover, current hypotheses have so far largely focused on neurons and overlooked astrocytes, which are key regulators of neuronal function underlying complex behaviors [4]. In this review, we will quickly summarize clinical evidence for NPS in ND patients. We will then focus on their replication in ND animal models and mention different behavioral tests used for NPS assessment. Then, we will present recent evidence showing astrocyte-dependent regulation of NPS in rodent models of depression. We argue that similar mechanisms of altered astrocyte-neuron crosstalk could underlie NPS in the context of ND and be targeted for therapy.

1. Neuropsychiatric symptoms: a shared feature across ND

NPS include depression, anxiety, apathy, agitation, irritability, sleep disturbances, disinhibition and hallucinations. They have been consistently described in ND patients and are in fact, increasingly included in diagnostic criteria [5]. NPS can appear at different disease stages but are prevalent in prodromal phases. In this review, we will focus on AD, PD and HD, in which depression, anxiety and apathy typically precede cognitive or motor symptoms. This has been particularly well characterized in PD, where patients frequently show anxiety and depression several years (sometimes decade) before diagnosis [6]. Unsurprisingly, NPS accelerate functional deterioration in ND patients. There is no clear consensus regarding the efficacy of antidepressants in patients with ND. Yet, selective serotonin reuptake inhibitors remain the most commonly prescribed antidepressants, due to their favorable side-effect profile [7].

So far, there is no causative evidence showing a direct link between ND pathological mechanisms and NPS. Most studies have focused on "usual suspects" involved in major depressive disorder (MDD) that can also be dysregulated in ND. These include: neurotransmitter (glutamatergic, GABAergic, dopaminergic) and neuromodulatory (serotoninergic, noradrenergic) systems and the hypothalamus-pituitary-adrenal axis [8-10]. Interestingly, ND have both critical differences (distinct pathological mechanisms, primarily vulnerable brain regions) and common features (abnormal

neuronal networks, neuroinflammation, misfolded proteins). So whether NPS are caused by ND-specific pathology in limbic brain areas or altered connections between ND-affected and limbic regions is not known.

2. Assessing neuropsychiatric symptoms in ND models

NPS in animal models mainly recapitulate features of depression including anxiety, anhedonia, apathy, decreased social interactions and passive coping. These symptoms can be assessed using multiple well-established tests (**Figure 1**). We will focus on rodent ND models, which are mostly used in preclinical studies and mention some results obtained in non-human primates.

ND mouse models display a range of NPS, replicating symptoms observed in ND patients (see extensive reviews for AD [9], PD [8] and HD [10], **Table 1**). Interestingly, transgenic models, neurotoxin models (e.g. MPTP, 6-OHDA for PD) and others such as amyloid-β oligomer infusion [11], all display NPS. Discrepancies in results shown in **Table 1** can stem from several causes. First, ND are progressive and studies performed at different disease stages sometimes gave opposite results. Second, studies have used males or females, which may produce conflicting results. Traditionally, behavioral testing has mostly been performed on males because of the supposed variability in female performances due to their ovarian cycle or higher basal anxiety but also because some behavioral tests have only been designed for males (e.g. female urine sniffing test) [12]. However, considering the higher prevalence of MDD and some ND in women, there is an increasing consensus that both sex should be systematically used in preclinical studies, with appropriate tests and measured outcomes [12,13]. Last, differences in mouse background strains, housing and experimental conditions between laboratories (e.g. light/dark cycle, diet, background music, light exposure) can change behavioral performances, for example by changing anxiety level baseline. Within a disease model, discrepancies can also appear in behavioral test interpretation. For example, some AD mouse models show increased time spent in the center at the open field test (an indication of low anxiety) but with hyperlocomotion, which instead could be interpreted as an anxious behavior. At the splash test, time spent grooming can be interpreted either as apathy (if decreased) or as obsessive-compulsive disorder-like behavior (if increased).

Most studies focused on a given type of NPS, and did not perform a comprehensive behavioral assessment on the same model. The use of test batteries is useful, as some NPS might be disease-specific (e.g. repetitive behavior in HD [14]). Performing multiple and complementary behavioral tests on the same animal also allows z-score calculations to identify potential behavioral patterns and facilitates comparison between cohorts [13]. The inclusion of positive controls (e.g. stress models), displaying altered performances to most of these tests would also be appropriate. This can be challenging to implement, especially because laboratories working on ND and psychiatric

disorders are usually distinct. Of note, the tail suspension test and the forced swim test, which were originally designed to replicate hopelessness observed in MDD patients, have been instrumental in developing anti-depressant therapy, but are now largely criticized from both an ethical standpoint and scientific relevance [13].

Developments in behavioral neuroscience converge towards new paradigms to measure "natural" behaviors in rodents, including group-living. Machine-learning tools allowing single animal tracking have recently been developed but their application to group-housed animals is still challenging [15]. Another example is the Souris city setup, which consists in a compartmentalized social cage where mice live in large groups for prolonged periods of time and are individually tracked through radio-frequency identification chips [16]. This setup allows the detection of specific and stable behavioral traits in individuals. This is of particular relevance for NPS, as inter-individual behavior tends to be highly variable and can even be used as a classifier (i.e. stress susceptible vs resilient mice). SmartCube® is another automated behavioral platform using computer vision and mechanical actuators to detect spontaneous behaviors and reactions to various stimuli in individual mice [17]. The AutonoMouse system allows the simultaneous training and testing of group-housed mice performing discrimination tasks [18]. Last, refined behavioral analysis of facial expressions and body postures, especially during social interactions are being actively developed [19]. Such tools are being characterized in normal mice with few examples of applications in models of psychiatric diseases. They need to be first characterized in "pure" models of depression/stress before being applied to ND models.

Some NPS such as psychosis might not exist or are more challenging to detect in rodents. Recent studies in mice reported hallucination-like percepts of auditory stimuli [20] and head-twitch response as a specific hallucinogen-induced behavior [21].

Last, non-human primate models of ND also show a variety of NPS. For example, MPTP-lesioned monkeys display apathetic behavior [22], anxiety, lack of motivation, excessive grooming [23] and hallucinatory-like responses to non-apparent stimuli [24]. Monkeys expressing mutant α-synuclein also show anxiety-related stereotypical behavior [25]; while HD transgenic monkeys display increased anxiety and aggression [26].

3. Astrocytes regulate neuronal function and animal behavior

Research on NPS has so far largely focused on neurons. However, recent studies show that non-neuronal cells such as astrocytes may also play a role in these symptoms. Astrocytes are key partners of neurons and fulfill many vital roles such as trophic and metabolic support; regulation of synaptic transmission; neurotransmitter reuptake or maintenance of K^+ and water homeostasis [27].

Thanks to the development of new tools allowing precise manipulation of astrocyte Ca^{2+} signaling, it is now well established that astrocytes regulate the activity of neurons involved in a myriad of behaviors including memory, motor control, feeding, fear or circadian rhythms [4]. Furthermore, recent evidence showed that astrocytes are not identical throughout the brain. Instead, they have brain region-specific features allowing tailored interactions with their neuronal neighbors [28]. This is particularly relevant for NPS that involve distinct, yet highly connected brain circuits [29]. ~~It is now well described that abnormal neuron-astrocyte crosstalk contributes to ND pathogenesis. For example in AD, several key astrocyte functions are altered and subsequently impact neuronal networks [30]. Restoring some of these functions in primarily affected brain regions can have beneficial effects on AD symptoms. However, such approaches have so far not been used to assess the specific impact on NPS in ND.~~ In fact, there is now multiple evidence showing that abnormal local astrocyte functions contribute to NPS in the context of MDD (**Figure 2**).

4. Astrocyte dysfunctions in MDD

Post-mortem studies show that astrocyte numbers are decreased in patients with MDD, although the extent depends on the brain region/subregion and method used to detect astrocytes [31]. This is associated with decreased expression of astrocyte-specific proteins including GFAP, connexins, glutamate transporters and glutamine synthetase. Yet, some other proteins enriched in astrocytes are upregulated in the brain and cerebrospinal fluid of MDD patients, including the inward rectifying K^+ channel 4 subunit 1 (KIR4.1) and the secreted protein S100β, respectively [32]. It is important to note that both proteins are also expressed in oligodendrocytes, in the human and mouse brain, so their dysregulation cannot be exclusively assigned to astrocytes. Interestingly, most of these findings are replicated in animal models of depression (see below). In recent years, single nuclei RNA sequencing revealed molecular correlates of many ND and MDD, with unprecedented resolution and showed that not only neurons but also glial cells display profound changes in their expression profile [33,34]. Recent studies also integrated data from genome-wide association studies with human brain proteome for both MDD [35] and AD [36]. Comparing such datasets could identify common dysregulated genes and pathways.

5. Local astrocyte dysfunctions can induce NPS

Recent work revealed that key astrocyte functions and signaling are involved in NPS (**Figure 2**). Here, we emphasize on innovative studies which used combinatorial, mostly astrocyte- and region-specific approaches. The majority of preclinical studies focused on depressive-like symptoms –

hereafter called NPS for clarity – which were mainly assessed using the forced swim test, the tail suspension, the sucrose preference test and the three-chamber test (**Figure 1**).

Ca^{2+} signaling and gliotransmission

Pioneering work showed that decreased vesicular release by astrocytes induces NPS and that ATP supplementation has anti-depressant effects in mouse models of chronic stress. This effect was replicated by activation of Ca^{2+}-dependent ATP release by astrocytes and subsequent activation of purinergic receptors P2X2 in the medial prefrontal cortex (mPFC) [37]. More recently, astrocyte release of ATP through the ion channel Calhm2 has also been associated with NPS. Astrocyte-specific knockout of *Calhm2* led to decreased ATP concentrations, loss of hippocampal spines and NPS in mice [38]. Moreover, Yu et al. used an original strategy to decrease astrocyte Ca^{2+} signaling via a plasma membrane pump, which constitutively extrudes cytosolic Ca^{2+}. Attenuation of Ca^{2+} signaling in striatal astrocytes was sufficient to trigger repetitive grooming (an obsessive-compulsive disorder-like behavior), associated with altered striatal neuron activity in freely behaving mice [14].

Ionic and metabolic homeostasis

Astrocyte may also impact NPS by regulating synaptic transmission through K^+ and glutamate homeostasis. For example, Cai et al. showed that astrocyte Kir4.1 levels are upregulated in the lateral habenula (LHb) in rodent models of depression. Virus-mediated increase in Kir4.1 expression in the LHb was sufficient to induce NPS in mice, while Kir4.1 downregulation (by a knockdown or a dominant negative form) rescued NPS in the congenital learned helplessness rat model of depression [39]. Another study showed that increasing levels of glutamate exchanger xCT in ventral dentate gyrus astrocytes by pharmacological and genetic approaches, reduced NPS induced by chronic restraint stress in mice [40].

Excessive avoidance behavior is a key feature of anxiety. Gomez et al. showed that photoactivation of astrocytes in the ventral tegmental area (VTA) promotes avoidance behavior by regulating glutamate-dependent drive on inhibitory GABA neurons, which reduces dopaminergic neuron activity. Interestingly, conditional knockout of the glutamate transporter GLT-1 in VTA astrocytes reduced avoidance but did not affect reward behavior [41].

Xiong et al. showed that epoxyeicosatrienoic acid (EET), an arachidonic acid metabolite, modulates astrocytic ATP release and NPS in a mouse model of chronic stress. Genetic manipulation to either reduce or enhance EET signaling specifically in mPFC astrocytes, impacted NPS in these mice. The astrocyte-specific enzyme involved in EET signaling was shown to regulate ATP-release from lysosomes, which in turn acted on purinergic receptors to modulate synaptic transmission [42].

Last, another recent study in the mPFC showed that neuron-astrocyte metabolic coupling regulates mouse passive coping response to stress induced by forced swimming. Lactate levels, as

measured by *in vivo* microdialysis, were increased in the mPFC of mice exposed to acute stress. Local virus-mediated knockdown in the mPFC of the astrocytic monocarboxylate transporter 4 (MCT4), which exports lactate in the extracellular space, decreased immobility duration at the forced swim test, interpreted as an abnormal passive coping strategy. On acute slices, MCT4 knockdown was shown to increase pyramidal neuron excitability. Thus, neuron-astrocyte metabolic coupling regulates mPFC neuron excitability and output response to stress [43].

Hormone signaling

Astrocytes express a variety of hormone receptors, which contribute to their interaction with neurons. Using astrocyte-specific, virus-mediated gain- and loss-of-function approaches in rats and mice, Wahis et al. showed that oxytocin receptor-mediated signaling induces Ca^{2+} signals in astrocytes and regulates central amygdala neuronal output through NMDA receptors co-activation via D-serine. Activation of oxytocin signaling reduced neuropathic pain-induced anxiety, through the astrocyte receptor. Interestingly, authors showed that only a subset of central amygdala astrocytes with distinct morphological features express oxytocin receptors [44]. Another study showed that astrocyte-mediated insulin signaling modulates NPS in mice. Inducible conditional knockout of insulin receptors in astrocytes induced several types of NPS. Virus-mediated cre-recombination in the NAc –but not the mPFC– increased passive coping at the forced swim test, without affecting anxiety. The lack of insulin signaling in astrocytes reduced ATP release, and subsequent dopamine-mediated activation of medium sized spiny neurons in the NAc [45].

Inflammation

Under various pathological conditions, astrocyte undergo a range of molecular, morphological and functional changes (i.e. they become reactive), which contributes to neuroinflammation and potentially impacts astrocyte-neuron crosstalk [30]. Nevertheless, the precise impact of astrocyte reactivity on NPS is still unclear. Leng et al. observed that in mice exposed to chronic unpredictable mild stress or injected with lipopolysaccharide that both trigger NPS, menin levels (encoded by *Men1*) were decreased [46]. Surprisingly, astrocyte- but not neuron-specific *Men1*-depleted mice displayed NPS, whereas memory performances were unchanged. Mechanistically, menin deficiency in astrocytes was found to activate the NF-κB pathway, which in turn triggered IL1β-mediated microglial activation and neuronal dysfunction.

6. Shared astrocyte-specific dysfunctions between MDD and ND

Strikingly, many of the astrocyte dysfunctions recently identified as leading to NPS are also involved in the pathophysiology of ND. These include altered Ca^{2+} signaling and gliotransmission,

abnormal ionic and metabolic homeostasis and inflammation [30]. These cellular alterations can go in opposite directions in NPS and ND (e.g., Kir4.1 function is increased in depression models whereas it is decreased in HD [47]) - which could be due to regional differences. Yet, their similarities strongly suggest that circuit-specific alterations of neuron-astrocyte crosstalk could be responsible for NPS in ND. Many studies have shown that restoring these astrocyte functions within primary vulnerable brain regions have beneficial effects on cardinal disease symptoms [30], but NPS were rarely assessed, except anxiety [48].

Conclusions

Astrocytes are not merely supporting cells for neurons but active and specific regulators of neuronal circuits controlling various behaviors. There is an increasing amount of evidence showing that replicating astrocyte dysfunctions observed in patients with MDD can cause in NPS in rodents. Because similar dysfunctions are often described in ND models, we suggest that they could underlie NPS associated with ND.

Yet, both fields of ND and neuropsychiatric disorders, have traditionally been neurocentric and for long neglected glial cells, such as astrocytes. The missing link(s) between astrocytes, NPS and ND need to be tackle with cell- and region-specific preclinical studies, on relevant mouse models with advanced behavioral profiling (**Figure 3**). Ultimately, the challenge will be to translate therapeutic astrocyte targeting to patients, to offer alternative options for NPS treatment.

ND model	Replicated pathology/ characteristics	Genetics	NPS			
			Anxiety	Anhedonia	Depression	Social interactions
Alzheimer's disease/tauopathies Reviewed in [9]						
Aβ oligomers infusion	Amyloid	Synthetic $A\beta_{1-42}$ peptide			↗	
APP/PS1	Amyloid fAD mutation	*APP_{Swe} different mutations in PSEN1*	↗/ =			↘ / = (age)
Tg2576	Amyloid fAD mutation	*APP_{Swe}*	↗/ =			↘
APP23	Amyloid fAD mutation	*APP_{Swe}*	↘ /=	=	↘ /=	
5xFAD	Amyloid fAD mutation	*$APP_{Swe/Fl/Lon}$ $PSEN1_{M146L/L286V}$*	=		↗/ ↘	=
3xTgAD	Amyloid, tau fAD mutation	*APP_{Swe} $PSEN1_{M146V}$ $MAPT_{P301L}$*	↗/ ↘/= (age, sex)	↗	↗	=
THY-Tau22	Tau	*$MAPT_{G272V/P301S}$*	=	↗	↗	
Parkinson's disease Reviewed in [8]						
6-OHDA	Neurotoxin Loss of DA neurons		↗		↗	↘
MPTP	Neurotoxin Loss of DA neurons		=		↗/=	
α-syn KO	α-syn loss of function	*SNCA $^{-/-}$*	↘ /=			↘
α-syn A53T	fPD mutation	*$SNCA_{A53T}$*	↘		↘	↘
LRRK2	fPD mutation	*$LRRK2_{R1441G}$* (BAC)	=		=	
VMAT2	Genetic elimination of dopamine vesicular stocks	*VMAT2 $^{-/-}$*	↗		↗	
MitoPark	Inactivation of mitochondrial transcription factor A (Tfam)	*Tfam cKO (DAT $^{+/Cre}$)*		↘		↘
Huntington's disease Reviewed in [10]						
R6/2	mHtt	Human *HTT* exon 1 155-165 polyQ			↗/ = (age)	
HdhQ111	mHtt	Chimeric human–mouse *Htt* exon 1 (knock-in) 109 polyQ	↗/ = (age)	↗/ = (age)	↗/ = (age)	
HdhQ140	mHtt	Chimeric human–mouse *Htt* exon 1 (knock-in) 140 polyQ			↗	
HdhQ175/(FDN)	mHtt	Chimeric human–mouse *Htt* exon 1 (knock-in) 175 polyQ	↗		↗	
HdhQ250	mHtt	Mouse *Htt* exon 1 (knock-in) 250 polyQ		↘	↗/ = (age)	
YAC128	mHtt	Full-length human *HTT* 120 polyQ (YAC)		↗	↗	
BACHD	mHtt	Full-length human *HTT* 97 polyQ (BAC)			↗/ ↘ (sex)	

Table 1. Summary findings of NPS in mouse models of AD, PD and HD. This table shows that NPS are robustly detected in most models despite their heterogeneous etiologies and the variety of models used (genetic or neurotoxin). Main effects explaining variable results are in brackets. Abbreviations: 6-ODHA: 6-hydroxydopamine, APP: amyloid precursor protein, BAC: bacterial artificial chromosome, DAT: dopamine transporter, fAD: familial AD, fPD: familial PD, Htt: huntingtin, LRKK2: Leucine-rich repeat kinase 2, MAPT: microtubule-associated protein tau, mHtt: mutant Huntingtin, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PSEN: presenilin, PolyQ: polyglutamine repeats, syn: synuclein, VMAT: vesicular monoamine transporter, YAC: yeast artificial chromosome. [49,50]

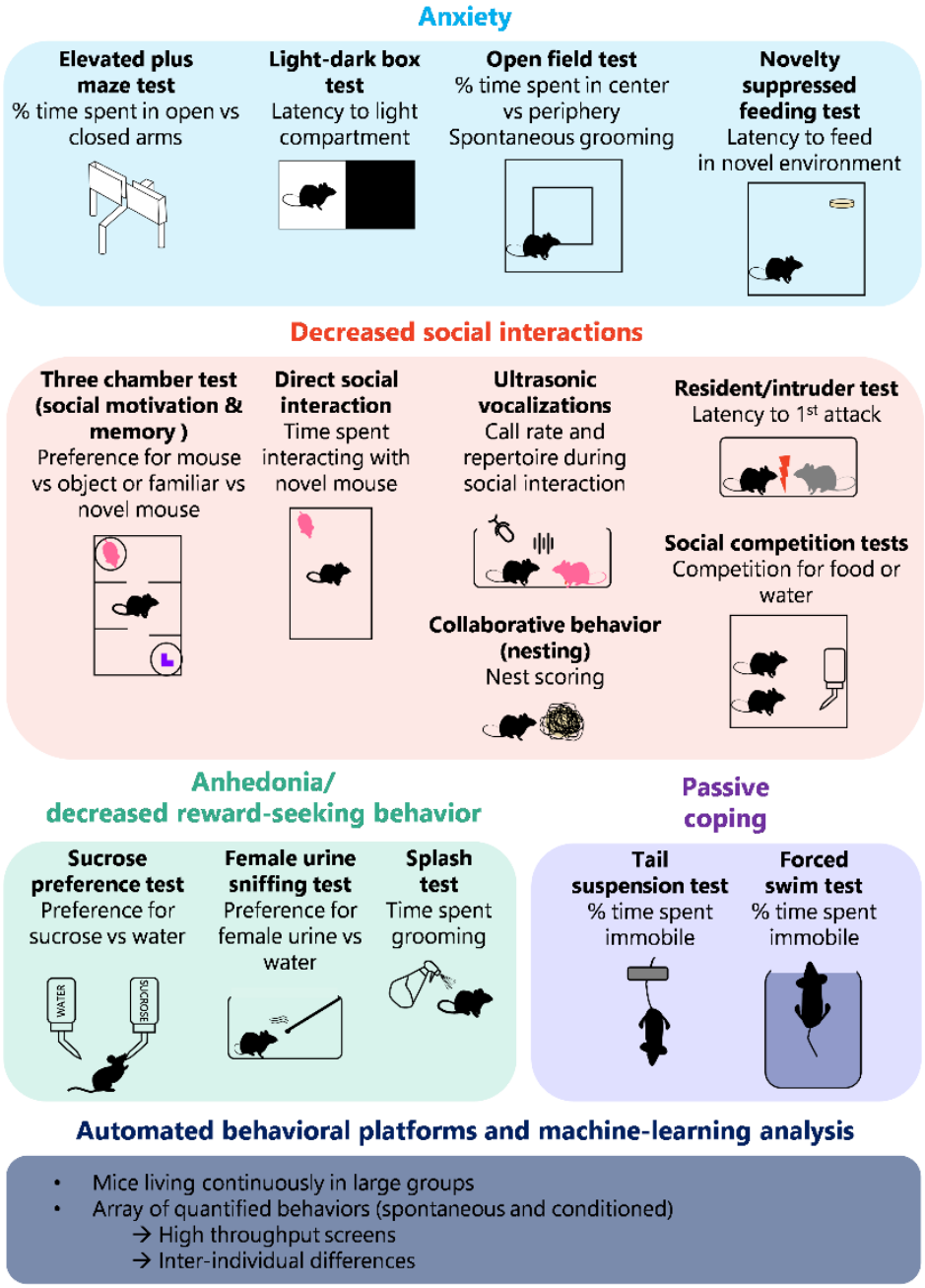

Figure 1. Tests and measured parameters for behavioral assessment of NPS in rodents. This figure depicts the variety of behavioral tests used to assess core NPS including anxiety (cyan), decreased social interactions (orange), anhedonia (green) and passive coping (purple). The dark blue panel summarizes newly-developed automated platforms and machine-learning based setups for high-throughput evaluation of behaviors in group-housed rodents.

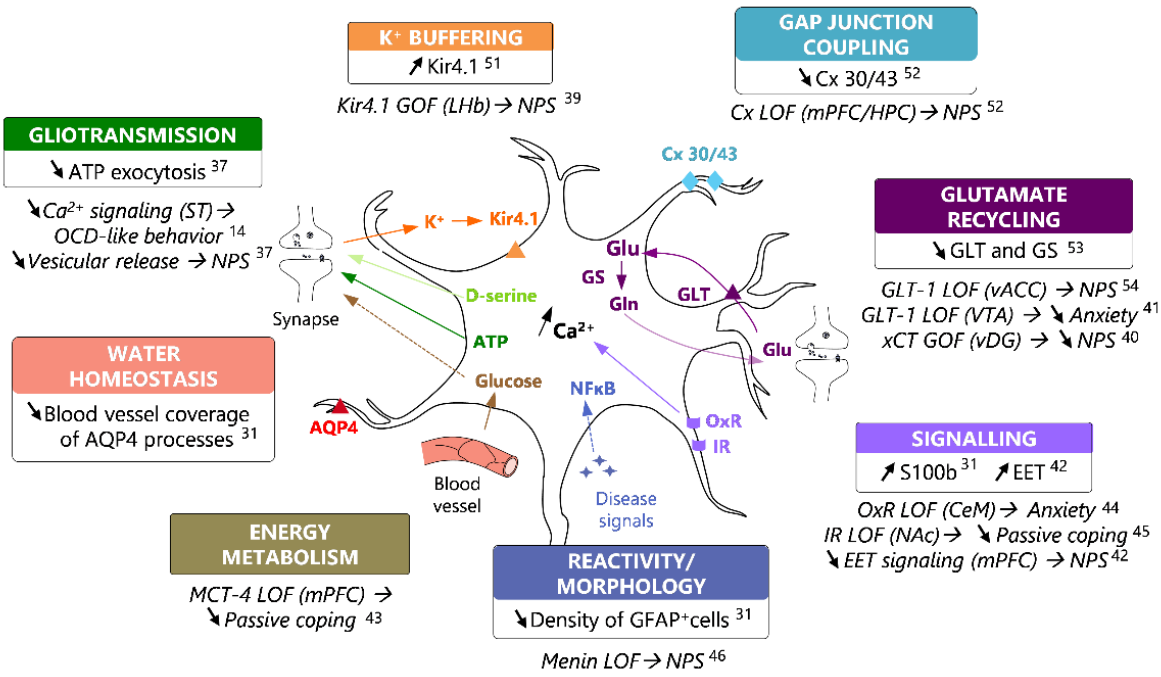

Figure 2. Key astrocyte functions are dysregulated in depression and their manipulation regulates NPS in rodent models. This figure summarizes recent findings linking astrocyte (dys)functions to NPS in animal models of depression. For each function (colored box), changes are data obtained in MDD patients and animal models of depression as compared with controls. For each function, text in italic below indicates manipulations of local astrocytes and their behavioral consequences on NPS (brain region in brackets). NPS refers to symptoms evaluated by a combination of tests (tail suspension test, forced swim, splash test, three-chamber test, open field elevated plus maze). If a single symptom was affected by the experimental manipulation, it is indicated (e.g. anxiety, passive coping). LOF (loss of function) /GOF (gain of function) refer to direct manipulation of the molecular target by knockdown/knockout or overexpression, respectively. ↓/↑ refer to the activation or inhibition of a cellular process (e.g. Ca^{2+} signaling).

Abbreviations: AQP: aquaporin, CeM: medial subdivision of the central amygdala central nucleus, Cx: connexin, EET: epoxyeicosatrienoic acid, GFAP: glial fibrillary acidic protein, GLT: glutamate transporter, Gln: glutamine, GS: glutamine synthetase, Glu: glutamate, HPC: hippocampus, IR: insulin receptor, Kir: Inward rectifying K^+ channel, LHb: lateral habenula, MCT: monocarboxylate transporter, mPFC: medial prefrontal cortex, NAc: nucleus accumbens, OxR: oxytocin receptor, OCD: obsessive compulsive disorder, ST: Striatum, vACC: ventral anterior cingulate cortex, vDG: ventral dentate gyrus, VTA: ventral tegmental area. [51–54].

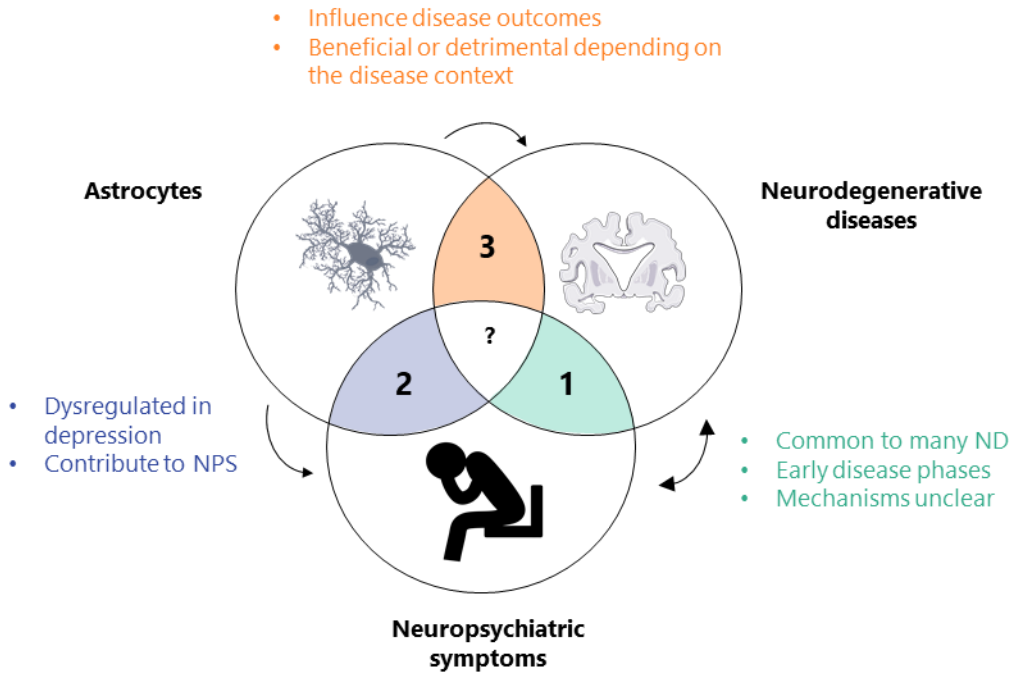

Figure 3. Astrocytes and neuropsychiatric symptoms in neurodegenerative diseases: exploring the missing links. 1. ND patients display NPS at early disease stages. 2. Recent evidence show that astrocyte dysfunctions are observed in MDD patients and in rodent models displaying NPS. 3. Similar astrocyte dysfunctions are also described in ND patients and animal models. Therefore, we suggest that astrocyte dysfunctions could contribute to NPS in ND.

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