Sex Differences in the Glial Pathology of Neurodegenerative Disease

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In recent years, studies of the sex differences in neurodegeneration have become more prevalent as the clinical values of developing individualized care have been ascertained. Neurodegenerative diseases are the most common age-related disorders involving abnormalities in the nervous system and brain function. Three common diseases are Alzheimer's Disease (AD), Parkinson's Disease and Amyotrophic Lateral Sclerosis. Although these diseases have different causes, they share some common features, including abnormal activity of glial cells. The sex differences which underlie neurodegenerative diseases could potentially be explained by the differences in glial cells. These disorders and glia have differences depending on the patient's sex, and this review aims to highlight the role of sex differences in glial cells in the manifestation and progression of these neurodegenerative diseases. A greater proportion of neuropathological disease-associated glia to homeostatic glia in females could be linked with the earlier and more severe onset of AD in females due to a diminished capacity for effectively clearing out amyloid plaque. In PD, aberrant glial activity at a higher incidence rate in males could be responsible for the diminished elimination of debris, α-synuclein aggregates, which could underlie the earlier onset and heavier prevalence of PD in males. ALS displays myelin damage, which could be caused by a higher proportion of disease-associated to homeostatic glia in males, potentially underlying the earlier onset and greater prevalence of the disease in males. Overall, glial cell differences could potentially explain the higher and more severe incidence of AD in women, as well as the earlier and more frequent incidence of PD and ALS in men.

Introduction

The prevalence of neurodegenerative diseases has been increasing; consequently, it has become more important to understand the underlying mechanisms of these disorders. Three of the most prevalent neurodegenerative diseases include Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS).

Alzheimer's disease (AD) is the most common neurodegenerative disease in the United States and typically affects patients of 65 years and older. The disease is characterized by the loss of neurons in the cerebral cortex and various subcortical structures. Additionally, it is informed by the abundance of amyloid plaques in the brain, which are misfolded protein aggregates that disrupt regular neuronal activity. AD affects females and males differently, with the disease being more prevalent and resulting in more significant cognitive decline in females when compared to males [1].

Parkinson's disease (PD) is the second most common neurodegenerative disease in the United States and typically affects patients of 60 years and older. It primarily occurs with a loss of function or death of dopaminergic neurons, resulting in a wide variety of motor deficits including rigidity, tremors, and bradykinesia. PD is also characterized by an abundance of α-synuclein (αSyn) aggregates which disrupt normal neural functioning. PD also affects females and males differently, as reflected by the early onset and increased prevalence in males compared to females [2].

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that primarily affects motor neurons, which are responsible for controlling voluntary movement. With the death and degeneration of motor neurons, over time symptoms include muscle atrophy, fasciculations and paralysis. Additionally, variations of the disease may cause patients to show signs of dementia and other neurocognitive deficits. The neurodegenerative manifestation of ALS is somewhat similar to PD, in that males display earlier onset of the disease than females [3].

Glial cells have increasingly become the target of investigation, as their role in neurodegeneration has been suspected. Sex differences have been observed in glial cell activity, and this review aims to highlight how those differences affect the pathology of AD, PD, and ALS.

Discussion

Classifications of Glial Cells and Their General Functions

Although glial cells were thought to be the most populous cells in the nervous system and to compose approximately 90% of the cells in the adult human brain, recent techniques have suggested a more even distribution to neurons [4]. The relative abundance of glia varies depending on which region of the brain they are found in, as the ratio of glial cells to neurons in the cerebral cortex gray matter is approximately 3:2, whereas

it is approximately 13:4 with both cerebral cortex gray and white matter combined[5]. The general function of glial cells is to support and nourish neurons, create synapses and maintain homeostatic equilibrium in the nervous system. Glial cells can be classified into three different categories based on their specialized functions; microglia, astrocytes, and oligodendrocytes.

Microglia

Microglia are glial cells often heralded as the macrophages of the central nervous system (CNS). Over the years, microglia have been classified by researchers independently according to various characteristics, leading to disagreement regarding nomenclature; however, recently there has been a push towards standardizing their nomenclature[6]. Here, we will refer to them by the two major classifications of homeostatic and disease-associated microglia (DAM). Homeostatic microglia are the most common form of microglia and are vital in synaptogenesis and synaptic plasticity. These microglia play various neuroprotective roles in healthy, non-diseased tissues, i.e clearing debris, expressing proteins etc. When transitioned to the DAM state, they display neuroinflammatory effects, indicating a potential loss of their critical functions and promotion of neurodegenerative effects and neuroinflammation. Thus, DAM can play various neurotoxic roles.

Astrocytes

Astrocytes, also known as astroglia, are star-shaped cells which are primarily responsible for providing nutrients to neurons, regulating ion concentration gradients, and providing structural support in the brain. When astrocytes become immunoreactive, they release cytokines, resulting in a local immune response. There has been extensive research conducted as to the subsets of astroglia with respect to their phases of activity. Here, we will refer to them as homeostatic astroglia and disease associated astroglia (DAA). Homeostatic astroglia are tasked with primarily neuroprotective roles, such as important regulation of neurotransmitters and metabolism, as well as protection against oxidative stress. In cases of neuroinflammation, DAA are potentially influential, as pathogenic stimuli affect astroglial function negatively resulting in a decrease in neuronal functionality[7]. Overall, the accumulation of DAA can be associated with neuroinflammatory and neurotoxic effects.

Oligodendrocytes

Oligodendrocytes are primarily responsible for myelinating neurons in the CNS, similarly to myelinating Schwann cells in the peripheral nervous system (PNS). The difference between these two cells; however, is that most oligodendrocytes are able to myelinate multiple neurons at once, whereas Schwann cells are only able to myelinate singular neurons at a time. Oligodendrocytes fall under four different classifications. Type I cells are responsible for ensheathing many smaller axons with myelin in diverse orientations; type II cells are responsible for ensheathing similar axons with parallel myelin segments; type III cells are responsible for ensheathing fewer, larger axons; and type IV cells are responsible for sheathing singular very large axons and are the most similar to Schwann cells[8]. Due to the role they play in myelination, damage to oligodendrocytes and hindrance of their function may result in the manifestations of neurodegeneration associated with slower signal transmission times.

Role of Glial Cells in Neurodegeneration

Alzheimer's Disease

DAM abundance was found to be much higher and localized in the regions surrounding amyloid plaques, indicating a link between AD progression and DAM abundance[9]. This suggests that either DAM are responsible for the accumulation of amyloid plaque or are potentially transitioned to inhibit plaque progression. Early accumulation of homeostatic microglia in AD patients has been shown to lead to slower disease progression, which indicates that microglia are responsible for clearing amyloid plaques in pathogenic brain tissue[10]. Homeostatic microglia appear to play a major role in disease prevention as they destroy pre-existing amyloid plaque aggregates. However, the higher incidence of neurotoxic DAM in later stages of AD suggests that the transition from homeostatic microglia to DAM results in a loss of function, and ultimately promotes neurodegeneration in AD patients. As such, the abundance of DAM as a transitionary product from homeostatic microglia can be associated with the neurocognitive manifestations of AD in clinical patients.

Clinical manifestations of AD in patients often include cognitive deficits and a diminished ability to complete regular tasks. Specifically, as the disease progresses there is a loss of working and declarative memory, as well as more severe memory loss[11]. These symptoms are informed by a marked synapse loss in patients. Synapses allow for the conversion of electrical signals into chemical signals, which then lead to cellular responses. Long-term memory formation has been linked to recurrent synaptic pathways and strengthening, leading to an ability to recall previous events or ideas[12,13]. Similarly, regular task completion has often been associated with sequential synaptic pathways, implying that an impairment in both faculties could be associated with supernumerary pruning of synaptic pathways. The link between the symptoms and synapse pruning suggests that the cells responsible for pruning could be linked to the overall symptomatic manifestation

of AD.

The complement system is widely regarded as the most important mechanism of synaptic pruning. The complement system cascade is the pruning of extranumerary synapses in the immature brain. Microglia and astroglia could be responsible for the complement cascade resulting in hyperactive synaptic pruning[14]. This suggests that the hyperactivity of microglia and astroglia could be responsible for the clinical manifestations of AD associated with synaptic pruning. Because these glia have neurotoxic effects, they can be considered DAM and DAA. Therefore, the hyperactivity of transitionary DAM and DAA can be causal agents for the neurocognitive deficits associated with AD.

Parkinson's Disease

The death of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which is responsible for relaying dopamine to the corpus striatum, leads to rigidity, tremors and bradykinesia. PD is also informed by alpha-synuclein (αSyn) overabundance. Jiao et al. showed that the overexpression of αSyn led to the aberrant regulation of long non-coding RNAs (lncRNAs), specifically the incidence of higher downregulation than upregulation of lncRNA expression[15]. lncRNAs are strands of RNA that are responsible for the regulation of gene expression at various levels, including transcriptional, translational, and post-translational levels. Particularly, they could play a role in inhibiting the synthesis of αSyn, as higher levels of neurotoxic proteins in PD brains are linked with downregulation of lncRNA. As such, a higher incidence of lncRNA downregulation can be linked to excessive expression of αSyn synthesis.

Upregulation of lncRNA has neuropathological implications in the realm of active gliosis and astrocytic activity. In another study, Han et al. showed that the overexpression of H19, a type of lncRNA, led to the activation of hippocampal glial cells in mice displaying epileptic behavior[16]. This overexpression is a byproduct of the physiological upregulation of the RNA strand, and thus suggests that upregulation of lncRNA may have implications for PD glia. Specifically, the study showed that this lncRNA led to a neuroinflammatory response, characteristic of neurotoxic microglia. Although this study was performed in epileptic mice, lncRNA misregulation has been associated with neurotoxic PD proteins, and thus can inform the role of microglia in PD. Therefore, induced neurotoxic gliosis in PD could be caused by lncRNA upregulation.

In addition to the effects on glial cells themselves, lncRNA downregulation has also been associated with overexpressive synthesis of αSyn. The synthesis of αSyn has historically been found to be greater in neurons than in astroglia; however, αSyn has been shown to be transferred to astroglia in aggregates[17]. Further, the astrocytic expression of PD-related A53T αSyn has been directly linked to neurodegeneration[18]. This suggests that αSyn expression could lead to the abnormal astroglial activity associated with PD, and ultimately that abnormal astrocytic activity could be an underlying cause for symptomatic PD. In a recent study, di Domenico et al. showed that astroglia in PD displayed aberrant autophagy, and led to control neurons displaying higher levels of αSyn themselves[19]. The findings of these studies seem to suggest a critical role of astroglia in the effects of αSyn aggregates, namely that the dysfunction of these astroglia could be linked to the clinical manifestations of PD neuropathology.

Amyotrophic Lateral Sclerosis

ALS is characterized by the loss of both upper motor neurons in the primary motor cortex and corticospinal tract projections, and lower motor neurons in the ventral horn of the spinal cord and the pontomedullary nuclei[20,21]. Upper and lower neurons form a two-neuron circuit and are responsible for causing a movement response to electric signals. Upper neurons project from the motor cortex to the brainstem and spinal cord, whereas lower neurons project from the spinal cord to muscles and glands, allowing for the actual response. As such, understanding the differences in deterioration of these neurons could yield valuable information on ALS sex-specific pathology.

Neuronal damage has historically been linked to excessive reactive astrogliosis and microgliosis, as those responses are typically neuroinflammatory, resulting in damage to surrounding neurons. ALS has two common classifications, sporadic ALS (SALS) and familial ALS (FALS). SALS is more common than FALS, and refers to the seemingly random and non-familial pathology of ALS[22]. FALS is the inherited form of ALS and has known genetic mutations involved, whereas SALS has unidentified mutations.

Microglial activation has historically been linked to the expression of CD-68, which is a protein found to be expressed by cells of macrophytic lineage. This protein is expressed in microglial lysosomes, which aid in phagocytizing debris. Additionally, this protein has been linked to the overexpression and neuropathological effects of microglia, termed microglial pathology. One recent study found that cases of ALS had high levels of CD-68 staining, indicating a high level of microglial activity[23]. This suggests that the pathology of ALS is at least in part influenced by microglia. Additionally, these reactive microglia have adverse effects on astroglial activity. Specifically, reactive microgliosis led to the transition of astroglia into their DAA state, which has historically been linked to the manifestation of various ALS symptoms[24].

In familial cases of ALS (FALS), it has been reported that mutations resulting in aberrant astroglial activity are responsible for neurotoxic effects representative of ALS pathology. A recent study found that FALS patients with mutated C9ORF72

(C9), a protein abundant in neurons, had abnormal astroglia which contributed to neuropathological effects via increased oxidative stress[25]. Astroglia have traditionally held roles in maintaining metabolic processes and pH homeostasis, and as such their linkage to mutations in a protein found in abundance within neuronal cells imply a related effect on neuronal pathology in ALS. In addition to being associated with mutations in the C9 gene, damage to astrocytes in FALS patients with dominant mutations in the superoxide dismutase (SOD1) gene are also associated with neuropathological effects in motor neurons[26]. In addition to aberrant astroglia, mutations in the SOD1 gene have also been linked to neurodegenerative effects in neurons expressing the gene themselves[27]. Because of the link to damage in astroglia, this suggests that mutations in the SOD1 specific to astroglia and motor neurons result in astroglial damage, and thus inform the neurodegenerative progression of FALS. Therefore, astroglial neuropathology is causal to the development of ALS.

Sex Differences in the Brain and Glial Cells

There has been much controversy over the years as to the specifics of differences between the male and female brain. Older studies have argued that there is no such thing as a sex-specific brain, with more recent studies adopting a more heterogeneous classification of brains[28]. Despite these seemingly contradictory ideas, there are definitive sex-specific differences associated with glial cells. Sex differences are present when it comes to different types of glia, resulting in altered neuroinflammatory reactions in males and females.

Glial Cell-Derived Sex Differences in Neurodegeneration

Glial Cell-Derived Sex Differences in Neurodegeneration

AD has definitive differences across the sexes. Namely, women tend to experience the disease more often, as well as display more rapid hippocampal deterioration[29]. This suggests that something in the affected female hippocampus has more rapid neurotoxic effects than in the male hippocampus. There are more microglia with thick, long processes in female mice hippocampal areas[30]. This morphology suggests DAM identity, and thus these microglia in the hippocampus may be neurotoxic. So, the higher number of DAM in the female hippocampus may be associated with the increased female hippocampal deterioration in AD. In addition to DAM, there may also be fewer homeostatic microglia in female hippocampi.

One study showed that female mice have greater numbers of astrocytes in the CA3 area of the hippocampus when subjected to corticosterone, via stress[31]. These astrocytes are most likely DAA, as they are more numerous in response to excess stress-a hallmark of neuroinflammation. Although female microglial cells appear to be neuroprotective in response to stress when compared to male cells, female astrocytes may not follow the same pattern[32]. Additionally, despite less severe immunoreactivity of LPS exposed female astrocytes than in males, those astrocytes are specifically homeostatic in response to LPS presence[33]. Toxins and neurogenic stress associated with AD, such as excess tau protein, are different in pathology and could explain the seeming contradiction between the seemingly more reactive female astrocytes in the hippocampus compared to female astrocytes that are less reactive to LPS. Additionally, there were more astrocytes in the male hippocampus hilus in response to LPS[34]. These astrocytes are most likely homeostatic in nature, and as such could inform the lower incidence rate in men. Thus, a higher incidence of DAM and DAA in female hippocampi could explain the more rapid hippocampal deterioration in females with AD.

It has been shown that microglia have both transcriptional and translational differences between men and women. Specifically, male microglia have higher levels of expression of myosin related proteins compared to female microglia[35]. Myosin is vital to cell stability and membrane vesicle tracking, and as such higher levels of myosin related proteins lead to potential differences in these very functions. Additionally, Myosin VI has been determined to colocalize with tau proteins in AD brains[36]. Hyperphosphorylation of tau proteins has been previously linked to oxidative stress[37]. Microglial cells in the homeostatic state are typically involved in expression of proteins, rather than facilitating an immune response. As such, these microglial cells' expression of tau proteins indicates that they are homeostatic in nature. The colocalization of Myosin VI and tau proteins in AD brains, in conjunction with this fact indicates that the higher concentration of homeostatic male microglia may be responsible for the overall lesser incidence of the disease in males. Thus, more homeostatic microglia in males may be associated with their lower AD rate.

Parkinson's Disease

Contrary to AD, PD is less prevalent in females and occurs at older ages than in males2. Potential reasons may lie in differential microglial pathology. One study found that microglial activation, i.e. the transition from homeostatic to DAM is inhibited by stress specifically in dopaminergic neurodegeneration[38]. In addition, one study found that both chronic and acute stress led to a significant decrease in microglial activation in female mice (higher proportion of homeostatic microglia to DAM), whereas no significant change in activation was found in males[32]. Corticosterone is a major hormone in the stress response, and as such can be used to describe the response as a whole. This suggests that corticosterone induced stress may be a primary factor in microglial deregulation for

females, and perhaps less so for males. Thus, corticosterone may be responsible for sex differences in microglial deregulation in response to stress- specifically that females are more susceptible to deregulation after stress exposure. Since excessive microgliosis has been thought to have neuroinflammatory effects, it is possible that the protective nature of corticosterone in females could delay neurodegenerative progression. This means that the female stress response is more neuroprotective compared to the male response, which is seemingly neutral. This could potentially explain why PD is less frequently diagnosed in females, as their microglia have more protective, homeostatic roles.

Similarly, it was found that male astrocytes had a more severe reaction to LPS than females[33]. Lipopolysaccharides (LPS) are molecules that are bacterial toxins, and have historically been used to model neuroinflammation due to its effects on the expression of various inflammatory mediators[39]. LPS-induced neuroinflammation has been shown to cause cognitive impairment, which is a hallmark symptom of various neurodegenerative diseases[40]. As such, sex-specific astrocytic responses to LPS can be used to inform the progression of neurodegeneration and why it may vary in males and females. IL6, TNFα, and IL1β are cytokines - molecules responsible for the inflammatory immune response in cells. It was shown that male astrocytes respond with higher levels of these cytokines to LPS presence, suggesting a more severe neuroinflammatory response than in females[33]. The higher rates at which neuroinflammatory markers were displayed by male astrocytes than female astrocytes suggests that there is more DAA in male PD neurodegeneration, which could potentially explain the higher incidence in males.

Amyotrophic Lateral Sclerosis

Similar to PD, ALS manifests more often in males and at a younger age than in females3. Oligodendrocyte degeneration has been implicated in ALS[41]. As such, differences in oligodendrocytes and their precursors could provide valuable insight into the sex-differences of ALS. The sex-differences of oligodendrocytes and their precursor cells has been understudied compared to their glial counterparts. The research that has been done suggests sexual dimorphism in oligodendrocyte precursor cell (OPC) transcriptomes. Female OPCs are more likely to proliferate and migrate, as well as be resistant to oxygen deprivation whereas male OPCs are more likely to differentiate and have a higher capacity for myelination[42]. OPCs proliferate into oligodendrocytes in response to experimental demyelination or developmental hypomyelination[43]. The higher capacity for proliferation of female OPCs suggests that they are more likely to respond to low levels of myelin in CNS cells. In ALS, it has been demonstrated that myelin damage is present in the late stages of the disease[41]. This suggests that there may also be damage in the earlier stages of the disease, just less prevalent. Due to the role of oligodendrocytes in myelination, the higher likelihood of oligodendrocyte maturation in females suggests that the lower incidence rate among females could be due to these glial cell differences.

Excessive astrogliosis could result in myelin damage, yielding a breakdown of the two-circuit motor neuron pathway and thus inducing symptomatic cause for ALS. Astrocytes in males displayed more severe neuroinflammatory effects in response to LPS[33]. This toxin, as previously established, has been used to model neuroinflammation and degeneration due to its ability to yield cognitive deficits. This suggests that these very reactive astrocytes could also have severe effects in response to other cues, inducing ALS pathology more easily and at a younger age for males than in females. Therefore, the higher incidence of neurotoxic DAA could be linked to the similar higher incidence of ALS in males.

Conclusions and Future Implications

Neurodegenerative diseases are incurable and treatment may only sometimes lead to noticeable improvements in quality of life and symptomatic regression. As such, it is more important to develop precise treatments that fit the individual, and not simply the symptoms or diseases. Due to the various sex-specific differences in these diseases, it is obvious that what may work for male patients may not work for female patients and vice versa. Furthermore, these differences only magnify the importance of specific treatments. Sex-specific treatments may serve as a baseline for individualized treatments, allowing the final medication or therapy to be as close to the specific individualized symptoms as possible, and thus allow for a higher likelihood for improvement of the patients quality of life. Therefore, the sex-specific differences in neurodegenerative disorder progression and symptoms are important when considering treatments and even potential cures for these various diseases.

Further research on the link between glial cell pathology and neurodegeneration should focus on the sex-specific aspects of such a correlation. There have been numerous sex differences reported in both glia and neurodegeneration, so drawing a more definitive link between the two could yield fruitful results.

In the case of AD, since the accumulation of tau proteins has been implicated in the disease, do females and males display differences in the activity of glial cells responsible for clearing those protein aggregates? If so, what steps can be taken to best address those differences in the pathology of the disease? Exploring this could provide valuable insight into both the pathology of AD, as well as potential treatments- leading to an ultimate increase in clinical prognoses and patient quality of life.

With PD, the aggregation of αSyn has been linked to disease progression and manifestation. Since glia are supposed to take up excess debris and clear them, how do sex-differences in their activity affect the relative abundance of these proteins in males and females? Answering this question could similarly provide valuable insight into PD pathology and treatments for the disease.

ALS is informed by the degeneration of motor neurons, which could be linked to abnormal glial cell pathology. Due to this role of glial cells, how do glial cells specifically act differently in males and females? Could this be used to inform the higher disease prevalence in males compared to females? Understanding these differences could inform future treatments, in that specific replacement therapies for aberrant glial cell activity could be determined.

Overall, exploration of the sex-specific differences in neuropathologies in controlled studies could provide numerous valuable insights into the progression and treatment of those diseases. As such, it should be considered in the context of glial cells, an integral component of these diseases.

Methods

This review was conducted by searching an online database of journal articles for relevant material spanning from late 2008 to 2022 and analyzing them accordingly within the context of sex-differences and neurodegeneration.

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References

1 K. Laws, K. Irvine and T. Gale, *Curr. Opin. Psychiatry*, **31**, 133–139.
2 G. Gillies, I. Pienaar, S. Vohra and Z. Qamhawi, *Front. Neuroendocrinol*, **35**, 370–384.
3 P. McCombe and R. Henderson, *Gend. Med*, **7**, 557–570.
4 C. Bartheld, J. Bahney and S. Herculano-Houzel, *J. Comp. Neurol*, **524**, 3865–3895.
5 F. Azevedo, L. Carvalho, L. Grinberg, J. Farfel, R. Ferretti, R. Leite, W. Filho, R. Lent and S. Herculano-Houzel, *J. Comp. Neurol*, **513**, 532–541.
6 R. Paolicelli, A. Sierra, B. Stevens, M.-E. Tremblay, A. Aguzzi, B. Ajami, I. Amit, E. Audinat, I. Bechmann, M. Bennett, F. Bennett, A. Bessis, K. Biber, S. Bilbo, M. Blurton-Jones, E. Boddeke, D. Brites, B. Brône, G. Brown, O. Butovsky, M. Carson, B. Castellano, M. Colonna, S. Cowley, C. Cunningham, D. Davalos, P. Jager, B. Strooper, A. Denes, B. Eggen, U. Eyo, E. Galea, S. Garel, F. Ginhoux, C. Glass, O. Gokce, D. Gomez-Nicola, B. González, S. Gordon, M. Graeber, A. Greenhalgh, P. Gressens, M. Greter, D. Gutmann, C. Haass, M. Heneka, F. Heppner, S. Hong, D. Hume, S. Jung, H. Kettenmann, J. Kipnis, R. Koyama, G. Lemke, M. Lynch, A. Majewska, M. Malcangio, T. Malm, R. Mancuso, T. Masuda, M. Matteoli, B. McColl, V. Miron, A. Molofsky, M. Monje, E. Mracsko, A. Nadjar, J. Neher, U. Neniskyte, H. Neumann, M. Noda, B. Peng, F. Peri, V. Perry, P. Popovich and Pridans, *Neuron*, **110**, 3458–3483.
7 M. Bélanger and P. Magistretti, *Dialogues Clin. Neurosci*, **11**, 281–295.
8 M. Simons and K.-A. Nave, *Perspect. Biol*, **8**, 020479.
9 H. Keren-Shaul, A. Spinrad, A. Weiner, O. Matcovitch-Natan, R. Dvir-Szternfeld, T. Ulland, E. David, K. Baruch, D. Lara-Astaiso, B. Toth, S. Itzkovitz, M. Colonna, M. Schwartz and I. Amit, *Cell*, **169**, 1276–1290 17.
10 S. Hickman, E. Allison and J. El Khoury, *J. Neurosci*, **28**, 8354–8360.
11 H. Jahn, *Dialogues Clin. Neurosci*, **15**, 445–454.
12 H. Viola, F. Ballarini, M. Martínez and D. Moncada, *Progress in Molecular Biology and Translational Science*, Elsevier, vol. 122, p. 391–423.
13 K. Radwanska, N. Medvedev, G. Pereira, O. Engmann, N. Thiede, M. Moraes, A. Villers, E. Irvine, N. Maunganidze, E. Pyza, L. Ris, M. Szymańska, M. Lipiński, L. Kaczmarek, M. Stewart and K. Giese, *Proc. Natl. Acad. Sci*, **108**, 18471–18475.
14 A. Stephan, B. Barres and B. Stevens, *Annu. Rev. Neurosci*, **35**, 369–389.
15 F. Jiao, Q. Wang, P. Zhang, L. Bu, J. Yan and B. Tian, *Behav. Brain Res*, **331**, 123–130.
16 C.-L. Han, M. Ge, Y.-P. Liu, X.-M. Zhao, K.-L. Wang, N. Chen, W.-J. Meng, W. Hu, J.-G. Zhang, L. Li and F.-G. Meng, *J. Neuroinflammation*, **15**, 103.
17 H.-J. Lee, J.-E. Suk, C. Patrick, E.-J. Bae, J.-H. Cho, S. Rho, D. Hwang, E. Masliah and S.-J. Lee, *J. Biol. Chem*, **12**, 285.
18 X.-L. Gu, C.-X. Long, L. Sun, C. Xie, X. Lin and H. Cai, *Mol. Brain*, **3**, 12.
19 A. Domenico, G. Carola, C. Calatayud, M. Pons-Espinal, J. Muñoz, Y. Richaud-Patin, I. Fernandez-Carasa, M. Gut, A. Faella, J. Parameswaran, J. Soriano, I. Ferrer, E. Tolosa, A. Zorzano, A. Cuervo, A. Raya and A. Consiglio, *Stem Cell Rep*, **12**, 213–229.
20 M. Turner and E. Verstraete, *Neurol. Neurosci. Rep*, **15**, 45.
21 M. Kiernan, S. Vucic, B. Cheah, M. Turner, A. Eisen, O. Hardiman, J. Burrell and M. Zoing, *The Lancet*, **377**, 942–955.
22 T. Siddique and S. Ajroud-Driss, *Acta Myol. Myopathies Cardiomyopathies Off. J. Mediterr. Soc. Myol*, **30**, 117–120.
23 J. Brettschneider, J. Toledo, V. Deerlin, L. Elman, L. McCluskey, V.-Y. Lee and J. Trojanowski, *Microglial Activation Correlates with Disease Progression and Upper Motor Neuron Clinical Symptoms in Amyotrophic Lateral Sclerosis. PLoS ONE 2012*, **7**, 39216.
24 S. Liddelow, K. Guttenplan, L. Clarke, F. Bennett, C. Bohlen, L. Schirmer, M. Bennett, A. Münch, W.-S. Chung, T. Peterson, D. Wilton, A. Frouin, B. Napier, N. Panicker, M. Kumar, M. Buckwalter, D. Rowitch, V. Dawson, T. Dawson, B. Stevens and B. Barres, *Nature*, **541**, 481–487.
25 A. Birger, I. Ben-Dor, M. Ottolenghi, T. Turetsky, Y. Gil, S. Sweetat, L. Perez, V. Belzer, N. Casden, D. Steiner, M. Izrael, E. Galun, E. Feldman, O. Behar and B. Reubinoff, *EBioMedicine*, **50**, 274–289.
26 K. Yamanaka, S. Chun, S. Boillee, N. Fujimori-Tonou, H. Yamashita, D. Gutmann, R. Takahashi, H. Misawa and D. Cleveland, *Nat. Neurosci*, **11**, 251–253.
27 F. Giorgio, M. Carrasco, M. Siao, T. Maniatis and K. Eggan, *Nat. Neurosci*, **10**, 608–614.
28 A. DeCasien, E. Guma, S. Liu and A. Raznahan, *Biol. Sex Differ*, **13**, 43.
29 B. Ardekani, A. Convit and A. Bachman, *J. Alzheimers Dis*, **50**, 847–857.
30 J. Schwarz, P. Sholar and S. Bilbo, *J. Neurochem*, 948–963.
31 N. Bridges, K. Šlais and E. Syková, *Acta Neurobioligiæ Exp*, **68**, 131–138.
32 J. Bollinger, C. Bergeon Burns and C. Wellman, *Brain. Behav. Immun*, **52**, 88–97.
33 M. Santos-Galindo, E. Acaz-Fonseca, M. Bellini and L. Garcia-Segura, *Biol. Sex Differ*, **2**, 7.
34 L. Saavedra, M. Hernández-Velázquez, S. Madrigal, A. Ochoa-Zarzosa

and L. Torner, *Psychoneuroendocrinology*, **126**, 105164.
35 D. Guneykaya, A. Ivanov, D. Hernandez, V. Haage, B. Wojtas, N. Meyer, M. Maricos, P. Jordan, A. Buonfiglioli, B. Gielniewski, N. Ochocka, C. Cömert, C. Friedrich, L. Artiles, B. Kaminska, P. Mertins, D. Beule, H. Kettenmann and S. Wolf, *Cell Rep*, **24**, 2773–2783 6.
36 S. Feuillette, V. Deramecourt, A. Laquerriere, C. Duyckaerts, M.-B. Delisle, C.-A. Maurage, D. Blum, L. Buée, T. Frébourg, D. Campion and M. Lecourtois, *Brain Res*, **1345**, 182–189.
37 Z. Liu, T. Li, P. Li, N. Wei, Z. Zhao, H. Liang, X. Ji, W. Chen, M. Xue and J. Wei, *Oxid. Med. Cell. Longev*, 1–12.
38 S. Sugama, T. Takenouchi, H. Kitani, M. Fujita and M. Hashimoto, *J. Neuroimmunol*, **208**, 104–114.
39 C. Batista, G. Gomes, E. Candelario-Jalil, B. Fiebich and A. Oliveira, *Int. J. Mol. Sci*, **20**, 2293.
40 J. Zhao, W. Bi, S. Xiao, X. Lan, X. Cheng, J. Zhang, D. Lu, W. Wei, Y. Wang, H. Li, Y. Fu and L. Zhu, *Sci. Rep*, **9**, 5790.
41 S. Kang, Y. Li, M. Fukaya, I. Lorenzini, D. Cleveland, L. Ostrow, J. Rothstein and D. Bergles, *Nat. Neurosci*, **16**, 571–579.
42 K. Yasuda, T. Maki, H. Kinoshita, S. Kaji, M. Toyokawa, R. Nishigori, Y. Kinoshita, Y. Ono, A. Kinoshita and R. Takahashi, *Stem Cell Res*, **46**, 101866.
43 L. Boshans, A. Sherafat and A. Nishiyama, *Neurosci. Lett*, **715**, 134593.