Introduction to spasticity and related mouse models

Frederique Wieters[1], Carolin Weiss Lucas[2], Matthias Gruhn[3], Ansgar Büschges[3], Gereon R. Fink[1,4], Markus Aswendt[1,4*]

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany

[2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Center of Neurosurgery, Cologne, Germany

[3]Department for Animal Physiology, Institute for Zoology, Biocenter Cologne, University of Cologne

[4]Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Center Juelich, Germany

*Corresponding author:

Markus Aswendt, PhD; ORCID: 0000-0003-1423-0934

markus.aswendt@uk-koeln.de

University Hospital Cologne

Department of Neurology

Kerpener Strasse 62

50937 Cologne

Germany

Abstract

Although spasticity is one of the most common causes of motor disability worldwide, its precise definition and pathophysiology remain elusive, which to date renders its experimental targeting tricky. At least in part, this difficulty is caused by heterogeneous phenotypes of spasticity-causing neurological disorders, all causing spasticity by involving upper motor neurons. The most common clinical symptoms are a series of rapid muscle contractions (clonus), an increased muscle tone (hypertonia), and augmented tendon reflex activity (hyperreflexia). This muscle overactivity is due to disturbed inhibition of spinal reflexes following upper motor neuron dysfunction. Despite a range of physical and pharmacological therapies ameliorating the symptoms, their targeted application remains difficult. Therefore, to date, spasticity impacts rehabilitative therapy, and no therapy exists that reverses the pathology completely. In contrast to the incidence and importance of spasticity, only very little pre-clinical work in animal models exists, and this research is focused on the cat or the rat spastic tail model to decipher altered reflexes and excitability of the motor neurons in the spinal cord. Meanwhile, the characterization of spasticity in clinically more relevant mouse models of neurological disorders, such as stroke, remains understudied. Here, we provide a brief introduction into the clinical knowledge and therapy of spasticity and an in-depth review of pre-clinical studies of spasticity in mice including the current experimental challenges for clinical translation.

Keywords

Spasticity

Stroke

Spinal cord injury

Multiple sclerosis

Amyotrophic lateral sclerosis

Upper motor neuron syndrome

Corticospinal tract

H-reflex

Neuroinflammation

Maladaptive plasticity

Objective

This systematic review was motivated by the urgent need to develop novel spasticity treatments. However, current knowledge is limited and mostly based on clinical observations and experimental work in the cat and rat model with focus on the spinal cord level (Sherrington, 1898). In contrast, more relevant, up-to-date studies in mouse models of neurological disorders are missing, as is the development of novel therapeutic approaches that specifically target the pathophysiology underlying spasticity. As we outline here, spasticity is central to many of the most frequent neurological disorders such as stroke and multiple sclerosis, which lead to primary or secondary damage of the motor system and particularly the pyramidal and extrapyramidal tracts. Surprisingly, the neuroanatomical substrate responsible for spasticity development in the case of a primary lesion affecting the central nervous system, e.g., an ischemic stroke, and the role of the imbalanced descending motor pathways, remain poorly characterized across species and diseases (Li and Francisco, 2015; Picelli et al., 2014). In this review, we introduce the basic concepts of current diagnosis and treatment of spasticity, followed by an in-depth review of animal experiments focusing on studies performed in mice and the existing challenges thereof.

We used the following search terms in combination with spasticity in the databases of PubMed and ISI Web of knowledge: Ashworth scale, amyotrophic lateral sclerosis (ALS), baclofen, botulinum toxin, cannabinoids, CNS stimulation, corticospinal tract (CST), Hoffmann's/H-Reflex, maladaptive plasticity, neuroinflammation, multiple sclerosis (MS), physiotherapy, spinal cord injury (SCI), stroke, traumatic brain injury (TBI). Genetic mouse models, as well as inducible disease models, were included (**Figure 1**).

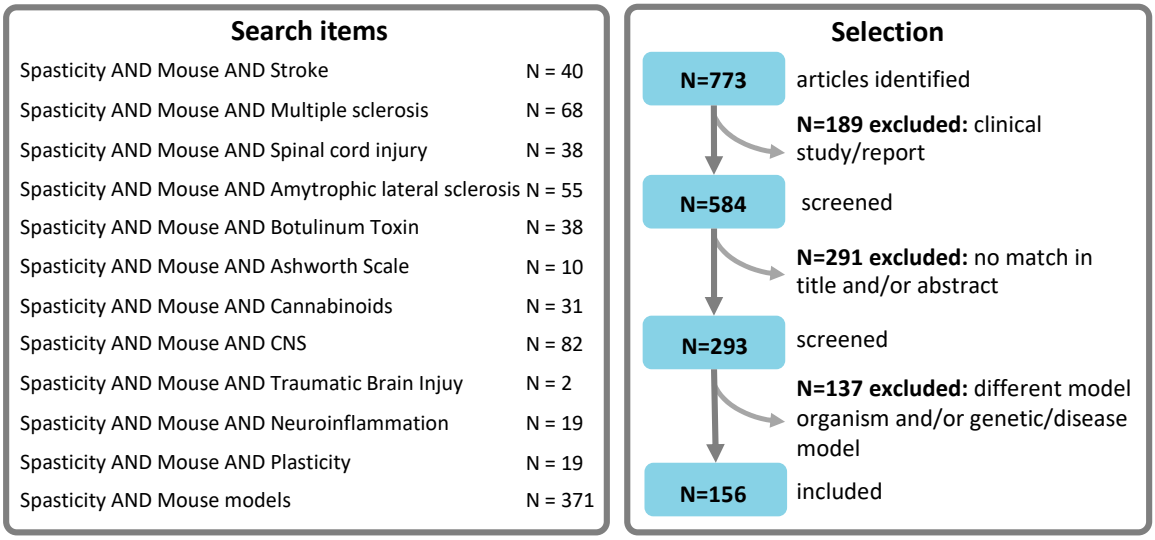

Figure 1: Systematic search and review process to identify all relevant mouse studies.

What is spasticity?

The definition of spasticity undergoes revisions and reconsiderations. According to a classical definition by Lance in the 1980s, spasticity is "a disorder of the sensorimotor system characterized by a velocity-dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome that does not include impaired voluntary movement and an abnormal posture" (Lance, 1990). In 2005, the spasticity study group "SPASM" (Support Programme for Assembly of a database for Spasticity Measurement) concluded that spasticity is "a sensorimotor control disorder that emerges as a result of an upper motor neuron syndrome and in the form of muscles' involuntary intermittent or permanent activation" (Burridge et al., 2005). Kheder et al. defined spasticity as a "disordered sensorimotor control, resulting from an upper motor neuron (UMN) lesion, presenting as intermittent or sustained involuntary activation of muscles" (Kheder and Nair, 2012). UMNs are responsible for initiating and modifying movements, and UMN lesions lead to clinical symptoms known as the upper motor neuron syndrome. The most common characteristics of UMN disease are muscle weakness (paresis), hyperreflexia, clonus, and spasticity (Emos and Agarwal, 2020; Mayer, 1997). Depending on the type and location of the UMN lesion, spasticity is often accompanied by a series of distinguished clinical signs (**Figure 2**). These include pathological reflexes (e.g., Babinski, Gordon), clonus (characterized by involuntary jerks of the limbs and evocable movements, e.g., by fast dorsiflexion of the foot and consequently stretching of the Achilles tendon), the clasp-knife phenomenon (characterized by a sudden decrease in muscle tone after an initially increased resistance in response to passive stretch), and spasms, as well as swallowing difficulties and dysfunction of the autonomic nervous system (Mukherjee and Chakravarty, 2010; Sheean, 2009). Spasticity develops over weeks and months following the initial lesion. While spinal cord lesions can quickly lead to severe spasticity, cortical lesions often result in weaker spasticity.

Incidence and economic burden

Similar to the broad range of definitions, spasticity is a result of a variety of damages to the spinal cord or the brain, of which the most common are: ischemic strokes, cerebral hemorrhage, traumatic brain injury (TBI), and spinal cord injury (SCI). Furthermore, spasticity occurs in neuroinflammatory diseases such as multiple sclerosis (MS) (Patejdl and Zettl, 2017)

or neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) (Chio et al., 2011b). Spasticity is one of the most common causes of physical disability worldwide, with an estimated incidence of at least 12 million patients. Spasticity develops in 35% of patients after stroke, 90% with cerebral palsy, 50% with TBI, 40% with SCI, and 37% - 78% with MS. The healthcare costs per patient are estimated to amount to 114,293€ per year (Svensson et al., 2014), whereby the severity of spasticity directly correlates with the societal and economic burden (Stevenson et al., 2015). In addition, there are the patient's productivity loss as well as indirect costs for family home care (Ganapathy et al., 2015). Moreover, spasticity-related movement impairments go along with the risk of falling and resulting fractures, associated with increased morbidity and mortality, and particularly impact elderly patients (Graham, 2013).

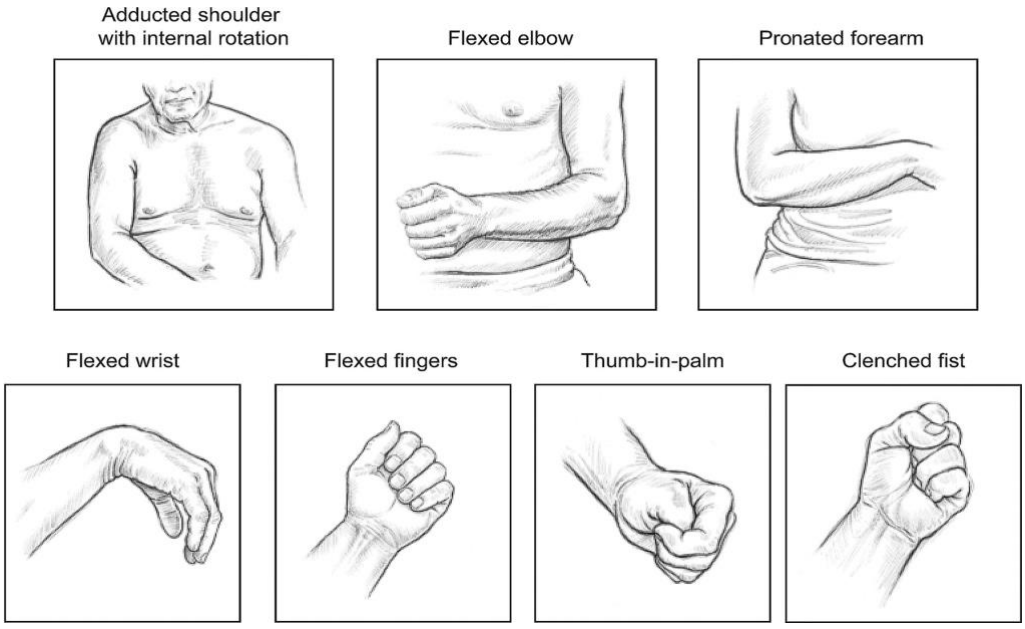

Figure 2: Common clinical signs of spasticity in the upper extremity resulting from an upper motor neuron lesion. Adapted from (Simpson et al., 2017) under the terms of the CC BY-NC-ND 4.0 license.

Mechanisms

The mechanisms underlying spasticity include the decreased inhibition of the spinal network (Delwaide and Oliver, 1988; Mazzocchio and Rossi, 1997), the increased excitatory synaptic inputs associated with Ia afferent fibers (Tan et al., 2012), and the increased motoneuron excitability (Bennett et al., 2004) (**Figure 3A**). Plasticity and neural remodeling processes, triggered by the initial damage, contribute to the time course of spasticity (Lang et al., 2013) and the adaptation of spinal inhibitory mechanisms (Ward, 2012). Cortical and internal capsular lesions such as in stroke damage not only the (pyramidal) corticospinal tract (CST) but

also the (extrapyramidal) corticoreticular excitatory input to the medulla. As a result, there is less inhibition through the dorsal reticulospinal tract (RST) and pronounced facilitatory input from the medial RST and the vestibulospinal (VST), which lead to an exaggeration of the stretch reflex (Trompetto et al., 2014) (**Figure 3B**).

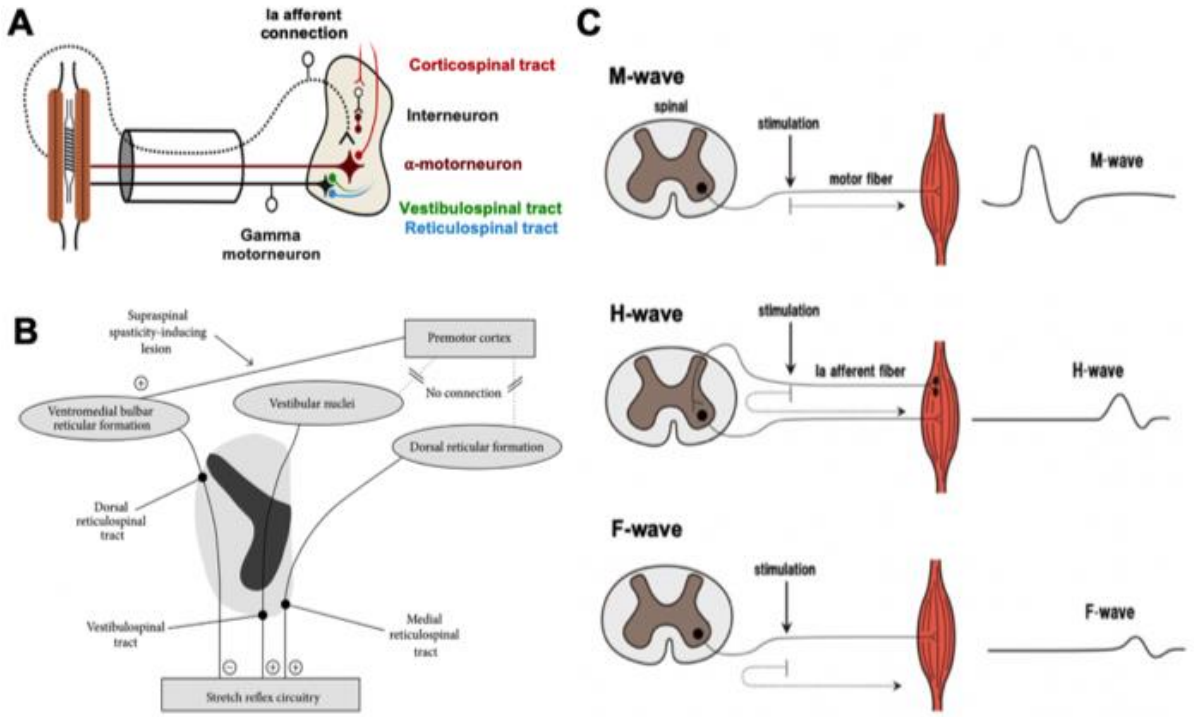

Figure 3: A) Afferent and efferent interconnection in the anterior horn. Upper motor neurons originate in the brain and brain stem and project to lower motor neurons within the spinal cord. The lower motor neurons originate in the ventral horn of the spinal cord: (1) alpha motor neurons project to extrafusal skeletal fibers and (2) gamma motor neurons project to intrafusal muscle fibers within the muscle spindle. A lesion of the CNS results in an interruption of the signaling from the upper motor neurons to the lower motor neurons or related interneurons (Lundy-Ekmann, 2002). Reduced presynaptic inhibition and hyperactivity of gamma motor neurons can lead to excessive signaling of 1a afferents from the muscle spindles, which triggers the continuous firing of alpha motor neurons, consequently leading to spasticity. **B) Schematic representation of the descending pathways modulating the stretch reflex circuitry.** In humans, two major descending pathways exist, the inhibitory dorsal reticulospinal tract and the faciliatory medial reticulospinal/vestibulospinal tract. In contrast to the vestibular nuclei and dorsal reticular formation, the ventromedial bulbar reticular formation is under direct cortical (premotor) control (adapted from (Trompetto et al., 2014) under the terms of the CC BY 3.0 license). **C) Evoked M-/H-wave response after electrical stimulation.** The M-Wave can be evoked by transcutaneous electrical stimulation of α-motor neurons and is directly measurable as action potentials of the skeletal muscle. The delayed H-wave is induced by electrical stimulation of the Ia axons from the muscle spindles and the resulting recruitment of α-motor neurons in the spinal cord. The F-Wave follows the H-Wave and allows assessing both efferent and afferent circuits of the α-motor neuron. M- and H- wave are, depending on the stimulus protocol and threshold often recorded together, the additional F-wave is recorded more rarely (adapted from (Satoru Kai 2013) under the terms of the CC BY 3.0 license).

Notably, neuroplasticity following CNS injuries can elicit beneficial effects like motor recovery while maladaptive plasticity results in the opposite effect including neuropathic pain, epilepsy, compensatory movements, and spasticity (Brown and Weaver, 2012) (Lundstrom et al., 2008) (Finnerup, 2017). Moreover, these processes can lead to muscle shortening, which further contributes to the motor impairments (Wahl and Schwab, 2014) and restricts mobility (Hughes and Howard, 2013). There is a time-limited period with elevated structural plasticity in the brain and spinal cord, e.g. after experimental sensorimotor stroke, in which the spinal plastic changes correlate with the severity of the cortical injury (Sist et al., 2014). Post-stroke recovery and spasticity are associated with different anatomical regions of plasticity. Thus, novel therapeutic approaches focus on cortical plasticity, and the hyperexcitability of the reticulospinal tract (RS) (Li et al., 2019). Recovery of motor functions is attributed to plastic reorganization, thereby the RS hyperexcitability may be the main reason for post-stroke spasticity (Li, 2017).

Neuroinflammation is one major driver for cellular, structural, and anatomical plasticity in response to the primary injury, such as in stroke, or as a major component of the disease, such as in multiple sclerosis (MS) (O'Reilly and Tom, 2020). Spasticity-related neuroinflammation, however, was so far only studied in MS, where it leads to dramatic changes in the ability of motor control, caused by reactive oxygen species, stress hormones, and cytokines (Ksiazek-Winiarek et al., 2015). For more information on spasticity mechanisms, we refer to the following reviews: (Burke et al., 2013; Dietz, 2008; Li and Francisco, 2015).

Clinical diagnosis

The clinical evaluation of spasticity comprises assessing patient-reported clinical findings, medication, and physical examination, as well as a series of neurophysiological tests (Hinderer and Dixon, 2001). The physical examination includes testing for the presence and frequency of flexor or extensor spasms, muscle tone, and tendon reflexes. In addition, voluntary muscle strength, contractures, functional loss, passive and active joint range of motion, sole reflex, triple flexion reflex, and clonus are analyzed (Burke et al., 2013). Quantitative evaluation of spasticity over time allows measuring treatment response. Such quantification can be achieved using clinical scales (Ashworth Scale, Penn Spasm Frequency Scale, Tardieu Scale, Barthel Index), walking analysis (e.g., kinematic and kinetic registration, dynamic EMG), neurophysiological methods (Hoffmann‘s reflex, M-wave amplitude), tendon reflex latency,

and biomechanical methods (isokinetic dynamometers, pendulum test) (Balci, 2018; Burridge et al., 2005; Sehgal and McGuire, 1998).

Ashworth Scale

The (modified) Ashworth (MAS) scale is the most widely used clinical spasticity scale. It was established to measure the course and the intensity of spasticity and the effect of therapy (Malhotra et al., 2008) for various clinical conditions such as stroke (Bakheit et al., 2003), spinal cord injuries (Akpinar et al., 2017), traumatic brain injuries (Allison et al., 1996), or multiple sclerosis (Haas et al., 1996). Because of its general definition and limitations, e.g., the nominal levels of the scale (Pandyan et al., 1999), the MAS has been criticized (Fleuren et al., 2010). For example, the MAS performs only moderately concerning the intra- and inter-rater reliability, showing worse reliability scores for the lower as compared to the upper extremity (Meseguer-Henarejos et al., 2018). This may partly be due to the lack of a clearly defined standard testing and rating protocol. Alternative scales for measuring spasticity are the Tardieu scale, which takes passive movement resistance at both slow and fast speed into account (Haugh et al., 2006), and the Penn spasm frequency scale, which counts the appearance and intensity of spasms per hour (Penn et al., 1989). However, these measures also lack reliability studies across various disorders.

Hoffmann's Reflex

The H-reflex (Hoffmann's reflex; named after the physiologist Paul Hoffmann) is triggered through the electrical stimulation of peripheral nerves (Hoffmann, 1910, 1918). The physiological response is recorded by electromyography (EMG) in one of the muscles supplied by the stimulated nerve. The stimulation causes orthodromic stimulation of α-motor neurons (MNs) and Ia-afferents (**Figure 3B**). It is achieved through transcutaneous stimulation or acutely applied or implanted extracellular nerve electrodes (Akay et al., 2014; Hultborn and Nielsen, 1996) The stimulation causes both, a direct muscle response (M-wave) and indirect, delayed activation of yet more α-MNs (H-wave), most of the time and depending on the stimulation protocol and thresholds for each wave, together in one trace (**Figure 3C**). As a standardized muscle stretch is difficult to achieve, the H-reflex, i.e., the electrical analog of the tendon jerk reflex, mediated through monosynaptic pathways in the spinal cord, is an additional method for quantifying spasticity. In spastic patients, an increased H-response

compared to an unaltered M-response and the ratio of the respective thresholds for both waves are considered for the maximum amplitudes and the slopes (Matthews, 1966). Electromyography (EMG) shows a decreased rate-dependent depression (RDD), thus reduced decline in the amplitude of the H-reflex over consecutive stimulations (Lamy et al., 2009).

Related neurological disorders

Spinal cord injury

There is a 65-78% risk of developing spasticity related to chronic spinal cord injury (SCI) more than one-year post injury (Adams and Hicks, 2005). Traumatic spinal cord injury leads to a loss of sensory and motor abilities of the affected body parts resulting from hyper-excitability of the spinal circuits (Andresen et al., 2016). The time course of spasticity in SCI typically follows a period of flaccid muscle paralysis and loss of tendon reflexes, termed spinal shock, in the first days to weeks after injury (Adams and Hicks, 2005). In the following weeks, spasticity-related reflexes appear, such as the tendon reflex, the flexor withdrawal reflex, and the Babinski sign. Maladaptive plasticity, e.g., enhanced excitability of motoneurons and interneurons as well as axonal sprouting of Ia-afferents and the formation of new synapses onto motoneurons, is the main target of current investigations (Elbasiouny et al., 2010), intending to recover lost spinal inhibition via assisted movements, pharmacology, or electrical stimulation (D'Amico et al., 2014).

Stroke

Stroke is one of the leading causes of long-term disability with a growing socio-economic burden (Pearson-Stuttard et al., 2016). Among other symptoms of post-stroke motor disorders, spasticity is a ubiquitous symptom with a prevalence that depends on the lesion location and ranges from 4-27% in the first four weeks to 17-43% in the chronic phase three months (Burke et al., 2013), and 37-40% 12 months after stroke (Opheim et al., 2014). Post-stroke spasticity (PSS) is observed more frequently in the upper than lower extremities (Lundstrom et al., 2010). PSS's clinical characterization includes urinary incontinence and impairments of gait, standing, sitting, and daily life tasks. Based on the location of the brain damage, various studies have shown that it is possible to predict if and how severely spasticity will occur (Picelli et al., 2014; Sunnerhagen, 2016) or the extent to which patients will recover after a stroke (Shelton et al., 2001).

Multiple Sclerosis

Multiple Sclerosis (MS) is a complex neuroimmunological disease with to date unclear causes. Due to progressive inflammatory demyelination of the central nervous system (CNS) and neurodegeneration at the later stages of the disease, it is the leading cause of non-traumatic disability among young adults. Symptoms include motor and sensory problems and depend on the location of the lesion. They reach from mild symptoms like loss of sensitivity, over muscle spasms to depression. The symptom that causes the severest disability in patients with multiple sclerosis is spasticity, which in 80% of these patients is the leading cause of disability (Patejdl and Zettl, 2017).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease. The loss of motor neurons results in progressive skeletal muscle weakness, atrophy, and, eventually, death due to respiratory muscle paralysis (Chio et al., 2012). The continuous degeneration of descending motor pathways of the spinal cord and the motor neurons in the anterior horn results in flaccid paralysis and simultaneous increase in muscle reflexes. Worldwide, the number of ALS patients is around 230,000 and expected to increase in the next decades due to the demographic change in aging societies (Arthur et al., 2016). About 40% of the patients with predominant upper motor neuron degeneration during ALS develop spasticity (Chio et al., 2011a). Combined electrophysiological and spinal diffusion tensor imaging (DTI) demonstrated a loss of large axons, and thus indicated a subclinical deficit in 85% of patients with ALS (Iglesias et al., 2015).

Therapy

Effective management of spasticity is necessary to reduce its devastating long-term effects. However, it is crucial to keep in mind that there is no therapy to cure spasticity and that the current therapies can be accompanied by considerable side effects such as muscle weakness. Furthermore, it can also be beneficial to maintain a certain level of spasticity, as increased muscle tone can have advantages when walking or standing. The current treatment is mainly focused on the reduction of symptoms and the improvement of mobility through physiotherapy. At present, the most common pharmacological therapy includes local intramuscular injections of the neurotoxin botulinum toxin to block synaptic transmission (Ward et al., 2003) and intrathecal targeting of the GABAergic receptors using the agonist baclofen (Heetla et al., 2014). Studies using neuromodulatory approaches (e.g., transcranial magnetic stimulation) that target the maladaptation of the system following the initial event

(e.g., stroke, SCI) remain scarce to date. Overall, low-frequency repetitive transcranial magnetic stimulation (rTMS) and cathodal transcranial direct current stimulation (tDCS) through the non-lesional hemisphere seem to be effective, especially when combined with other conventional therapies such as physiotherapy (Leo et al., 2017). Finally, neurosurgery provides transient and permanent denervation procedures, e.g., by localized injection of a neurolytic agent to cause demyelination and axonal destruction (Gras and Leclercq, 2017), or non-selective dorsal rhizotomy as well as peripheral neurotomy (Warsi et al., 2020).

Mouse models of spasticity

The first experiments studying spasticity were based on animal models using cats and rats (Ritz et al., 1992). In mice, spasticity is understudied, although mouse models are widely used for the investigation of the pathomechanisms underlying spasticity-relevant neurological disorders (Genc et al., 2019). We identified a limited number of studies using mice to model spasticity related to stroke, multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury and genetic manipulation (**Table 1**).

Stroke

Depending on the size and location of the lesion, stroke often leads to an imbalance of excitatory and inhibitory neuronal activity resulting in spasticity (Sunnerhagen, 2016). To date, only two studies have shown spasticity in the rostral and caudal forelimb area after cortical lesions induced by photothrombosis (Lee et al., 2014; Toda et al., 2014). In these studies, the rate-dependent depression (RDD) of the H-reflex in the affected and unaffected little finger muscle (*abductor digiti minimi*) was measured over eight weeks. As a result of the cortical lesion, the excitability of the affected muscles was increased compared to the sham-operated mice, and RDD was reversed by the anti-spastic drug baclofen one week after stroke induction. However, apart from the change in RDD over time, this model did not show correlations with the behavior.

Multiple Sclerosis

In experimental autoimmune encephalomyelitis (EAE), the mouse model of multiple sclerosis, spasticity spontaneously develops over weeks and months, as shown by several studies (Burrows et al., 2019; McCarthy et al., 2012; Robinson et al., 2014). The EAE model is a T-helper cell-mediated autoimmune disease characterized by monocyte and T-cell infiltration into the

CNS, followed by local inflammation, which results in primary demyelination of axonal tracks, impaired axonal conduction, and progressive hind-limb and lower body paralysis (Robinson et al., 2014). A combination of melatonin and baclofen (Ghareghani et al., 2018a), as well as CB_1 cannabinoid receptor agonists, showed promising results in ameliorating spasticity and tremor (Pryce and Baker, 2007).

Amyotrophic lateral sclerosis

As mentioned above, ALS impedes voluntary movements of the affected muscles and leads to paralysis or death within 2 to 5 years of diagnosis (Mitchell et al., 2010). ALS is related to several genes (Chia et al., 2018) and different mutations in the mitochondrial DNA (Borthwick et al., 2006). Common genetic mouse models include for example: superoxide dismutase 1 (SOD1) (Gill et al., 2019), TAR DNA-binding protein 43 (TDP-43) (Wils et al., 2010), ubiquilin-2 (UBQLN2) (Renaud et al., 2019), and alsin (ALS2) (Yamanaka et al., 2006). One common hypothesis for the underlying motor neuron vulnerability is susceptibility to excitotoxicity and oxidative damage (Robberecht, 2000). Treatment with Δ^9-THC led to delayed ALS progression in SOD1 mice and increased survival (Weydt et al., 2005). Overexpression of SOD1 leads to a loss of motor neurons, progressive paralysis, reduced lifespan, axonal denervation, and protein aggregation in the mouse model and ALS patients (Philips and Rothstein, 2015). There is also evidence for degeneration of serotonergic neurons in the brainstem and spinal cord before that of motor deficits (Fink, 2013). TDP-43 mice show a dose-dependent degeneration of cortical and spinal motor neurons leading to spastic quadriplegia as in ALS patients. Like ALS patients, TDP-43 mice accumulate ubiquitinated and phosphorylated TDP-43 in the nucleus and cytoplasm (Wils et al., 2010).

Spinal cord injuries

In animal SCI models, mostly rats (Zhang et al., 2014), which focus on the cervical region, the white matter disruption leads to spastic paralysis below the injury. A transection is uncommon, and the experimental contusion model is more comparable to the situation in humans (Hodgetts et al., 2009). The Basso Mouse Scale (BMS), an open-field locomotion test to analyze locomotion and hindlimb functions as well as gait abnormalities (Basso et al., 2006), allows assessing functional recovery in the mouse SCI model. Spinal-to-sciatic direct current stimulation (DCS) has been used in mice with SCI to reduce muscle hypertonia and hypotonia (Ahmed, 2014).

Genetic spasticity models not related to neurological disorders

The *spastic* mouse was discovered by random breeding (Chai, 1961). It carries a single-locus recessive mutation on chromosome 3 and develops a tremor as well as abnormal gait and reflexes within the first three weeks after birth. It was well characterized electrophysiologically (Biscoe and Duchen, 1986; White and Heller, 1982) and has been used for pharmacological studies (Biscoe and Fry, 1982). A significant finding was that spasticity results from a lack of glycinergic and GABAergic inhibition and, thus, an imbalance of inhibitory and excitatory activity in the spinal cord (Biscoe et al., 1984). Consistent with these findings, drugs that enhance synaptic GABA-ergic action reduce spastic symptoms in the spastic mouse (Becker et al., 1986; Biscoe and Fry, 1982). The gait of the spastic mice was described by short hind leg stride length ("hopping") and short footprint length (tiptoe walking) with periodic tremors during walking compared to the wild-type controls (Vignaud et al., 2019).

Other genetic mouse models focus on the effects of Selenoprotein P (SEPP), a selenium-rich plasma protein. SEPP delivers selenium from the liver to the brain. The groups of Hill (Hill et al., 2003) and Schomburg (Schomburg et al., 2003) produced mice with deletion of the SEPP gene and observed that the $SEPP^{-/-}$ mice had lower brain selenium concentrations than $SEPP^{+/-}$ and $SEPP^{+/+}$ and developed neurological dysfunction including spasticity with extended limbs and an inability to walk. The potassium-chloride cotransporter 2 (KCC2) is also suspected of contributing to the development of spasticity. KCC2 is a significant chloride extruder and responsible for maintaining the chloride homeostasis in mature neurons (Chamma et al., 2012). A downregulation of KCC2 has been demonstrated in amyotrophic lateral sclerosis (Fuchs et al., 2010), neuropathic pain (Coull et al., 2003), and cerebral ischemia (Jaenisch et al., 2010). Further, the down-regulation of KCC2 seems to contribute to spasticity after SCI (Boulenguez et al., 2010).

Challenges for investigating spasticity in mice

Compared to other aspects of the upper motor neuron syndrome or spasticity-relevant neurological disorders in general, the research output on spasticity in mice is minimal. There seems to be an experimental roadblock, which impedes further studies. We believe that there are three fundamental challenges for investigating spasticity in mice, which need to solved to generate reliable mouse models: 1) a standardized neuroscore, e.g., based on behavioral assessments optimized for specific neurological disorder models, 2) a standard protocol for the

H-reflex measurement and analysis, and 3) a better understanding of the common and differential roles of the pyramidal and extrapyramidal tracts between mice and humans in (recovery of) motor control.

Behavioral scoring

According to our literature research, there is no standard measure in rodents – especially in mice. Reports of clinical signs of spasticity such as a flexed elbow and forepaw are rare (Baker et al., 2000). Despite the genetic model, i.e., the spastic mice, characterized by a reduced muscle growth compared to wild type mice (Ziv et al., 1984), there are no reports in mice that investigated muscle spasms or increased muscle tone using force measurements and electromyographic recordings, as it has been reported in the well-established spastic rat tail model (Bennett et al., 1999). Furthermore, unlike in rats, where, for example, the swimming test was used to monitor spastic behaviors (Ryu et al., 2017), behavioral tests evaluating spasticity are lacking in mice. Several attempts have been made to quantify the behavioral deficit with other indirect measures, e.g., the gait (Vignaud et al., 2019). However, there is no standardized protocol or composite scoring available that would allow researchers to rate the spasticity level in a particular mouse model as it can be done with the Ashworth Scale in patients. To overcome this limitation, a test battery for motor control should be used that shows impairments and recovery over several weeks to months and includes tests for locomotion, strength, balance/coordination, and endurance. Despite the obvious differences in behavioral assessment between mice and humans, e.g., considering walking or task-related movements, there is considerable overlap of cellular mechanisms to allow finding cross-sectional changes in motor function, as it has been done for age-related changes in motor function (Justice et al., 2014). Notably, the validity of the neuroscore derived from these measures requires validation against clinical measures and multiple spasticity-related diseases.

Electrophysiology

In order to discriminate spasticity-related impairment from the primary disease-related impairment, electromyography (EMG) and electrophysiological measurements (H-reflex) are required. In anesthetized rats, it is possible to measure the muscle resistance in the lower limb during a step-by-step ankle rotation with variable velocity using simultaneous EMG recordings (Kakinohana et al., 2006). Such a system could provide a quantitative assessment with fewer

variables and sources of errors than a battery of behavioral tests. However, such a system is not yet established in mice, and the effects of muscle relaxant anesthetics need to be considered. Similarly, the H-reflex measurement and analysis is not straightforward. According to our own experience, measuring the H-reflex in patients is time-consuming and rarely used in clinical routines. Targeting the upper or lower limb nerves with needle electrodes in mice is even more difficult and variable, which could explain why we found only a few studies with EMG recordings included. Notably, custom-made and lightweight implantable nerve cuffs, wires, and tethers permit long-term continuous recordings of spontaneous and nerve-evoked EMG in mice (Carp et al., 2005). However, the electrode setup requires a difficult surgery and has not become a standard measurement to date. Furthermore, there is no standardized measurement protocol available so far. In mice and rats, the M-wave is often recorded at lower stimulus intensities and thus appears before the threshold for the generation of the H-wave is reached (Matthews, 1966). The reason for this observation remains unclear but may originate from different axonal diameters between these two species and humans. Besides, in mice and rats, the H-wave sometimes does not disappear at maximum M-wave amplitudes. This finding may result from the F-wave interference, which is caused by a returning action potential from the soma of the motor neurons after antidromic α-MN stimulation (Magladery and Mc, 1950).

Descending motor pathways

Finally, the current approaches to induce spasticity in mice might be impaired by the notion that it is necessary to target the same descending fiber tracts as in the human. However, the CST in humans seems to play a greater role in the development of spasticity than in rodent models, and its function must be understood first (Lemon, 2010; Welniarz et al., 2017). The macaque (pyramidal) corticospinal tract (CST) originates to 30%-40% from the primary motor cortex and to 60-70% from the supplementary motor area (SMA), premotor cortex (PMA), parts of the somatosensory areas (S1 and S2) and parts of the posterior parietal cortex (Moreno-Lopez et al., 2016). The CST is essential for voluntary movement and in higher primates for the hand dexterity control (Tohyama et al., 2017). A recent viral tracing study in mice suggests that in contrast to higher primates, connections between the motor cortex and motor neurons in the spinal cord are monosynaptic only until postnatal day 14. In the mouse, these cortico-motorneuronal (CM) connections start to form but become actively eliminated by Sema6D-PlexA1 signaling during development (Gu et al., 2017). One possible explanation

for the different CM connections in mice comparison to higher primates may be that increased manual dexterity confers no fitness advantages to quadrupedal animals. The topography of the descending CST is different between rodents and higher primates. The descending trajectories in higher primates run within the ventral and lateral funiculi of the spinal cord, whereas they run within the dorsal funiculu in rodents (Lemon, 2008). Furthermore, the amount of CST axons, that cross the midline at the level of the pyramids in the medulla varies across species, ranging from 80%-95% in rodents (Joosten et al., 1992), 90% in cats (Armand and Kuypers, 1980), 85%-90% in macaque and rhesus monkeys (Rosenzweig et al., 2009), to 75%-90% in humans with a high amount of interindividual differences (Jang, 2014). The remaining uncrossed part of the CST plays a clinical role for motor recovery, e.g., after stroke (Carmel and Martin, 2014). Unilateral absence of the CST input, caused by stroke or other lesions, can lead to downstream functional and morphological changes at the level of the spinal cord (Karbasforoushan et al., 2019). Most importantly, the imbalance of the corticospinal tract and the vestibulo- and reticulospinal tract contributes to spasticity, specifically the exaggerated stretch reflex in humans (Oudega and Perez, 2012; Sangari and Perez, 2019). Selective damage to the pyramidal tract only produces weakness, loss of dexterity, hypotonia, and hyporeflexia, but no spasticity (Bucy et al., 1964). However, lesions, e.g. in the anterior limb of the internal capsule with fibers from premotor areas, tend to be associated with spasticity (Trompetto et al., 2014). As described above, only the premotor cortex has direct control over the dorsal reticulospinal tract (RST) by inhibiting the spinal reflex circuit, which is different from the excitatory inputs of the medial RST and vestibulospinal tract (VST). Similar studies are not available in rodents, particularly in mice. The origin and location of the reticulospinal and vestibulospinal tract were only described in cats and only recently supported by detailed tracing studies of the location and topography in the spinal cord (Watson and Harrison, 2012). Although the spinal tract anatomy – excluding the CST – is believed to be very consistent across vertebrates, it remains to be shown that the interplay of inhibitory and excitatory inputs to the spinal reflex circuits act similarly - especially after lesions and/or degeneration.

Conclusion and outlook

The molecular basis and the pathophysiology of spasticity are complex and incompletely understood. Further, to date spasticity treatment remains insufficient, with many patients being left with a severe disability. There is already a well-described mouse model available for almost all spasticity-related neurological disorders, either by genetic engineering or localized lesioning. However, since the discovery of the spastic mouse more than 30 years ago, only a minority of studies were carried out to target spasticity, especially related to stroke. Experimental modeling of spasticity in mice remains tricky due to an incomplete understanding of the differences in the role of descending fiber tracts for motor control, and no consensus or extensive evaluation of behavioral and electrophysiological scorings. Future studies are needed to assess all relevant aspects of spasticity with standardized readouts for the behavioral and electrophysiological evaluation that can be applied longitudinally for several weeks to months in large cohorts. By overcoming the current experimental hurdles of spasticity in mice, future studies would benefit from the rich portfolio of cutting-edge neuroscience tools such as viral tracing and optogenetics, for the anatomical and functional dissection of spasticity-related circuits in the mouse model (Wahl et al., 2017) (Liske et al., 2013). For example, these tools could be used to evaluate the modulation of the reticulospinal tract as suggested by clinical studies to improve motor recovery by reducing the excitability and connectivity in overactive neural circuits such as the stretch reflex (Moritz, 2018). Furthermore, molecular imaging and genetic targeting in the mouse model could provide a way to unravel how the neuroinflammatory response affects the development of spasticity, for example by longitudinal in vivo imaging of microglia by positron emission tomography (PET) or bioluminescence imaging (Belloli et al., 2018) (Collmann et al., 2019). The time profile of neuroinflammation assessed with such an imaging approach combined with a selective depletion of microglia (Elmore et al., 2014) could be used, for example, to investigate the beneficial effects on spasticity by reducing inflammation as suggested in clinical studies of immunotherapy to treat MS (Patejdl and Zettl, 2017) (Bergamaschi et al., 2011).

Spasticity-related biomarkers identified by experimental studies will be essential to validate clinically-relevant signs of spasticity when developing novel, urgently needed therapies that target the underlying pathophysiology.

Table 1: Mouse models of spasticity

Disease	Strain	Measurement	Phenotype	Treatment	Ref.
Stroke	C57BL/6J	RDD (H-reflex)	-	-	(Toda et al., 2014)
	C57BL/6J	RDD (H-reflex)	-	Baclofen	(Lee et al., 2014)
Multiple Sclerosis (EAE model)	Biozzi ABH	Force measurement of the leg, visual control of tail flicking and curling	Tremor with a persistent frequency of ~40 Hz	Cannabinoid receptor agonist(R(+)-WIN 55,212; THC methan-andamide	(Baker et al., 2000)
	C57BL/6	Clinical score	-	Melatonin, Baclofen	(Ghareghani et al., 2018b)
	C57BL/6, *Mir21*$^{-/-}$	Clinical score	-	THC; CBD	(Al-Ghezi et al., 2019)
Amyotrophic lateral sclerosis (ALS)	hSOD^{G93A}	Rotarod	No changes in motor behavior	-	(Weydt et al., 2005)
	SOD1^{G86R}	EMG of the tail muscle	Abnormal gait and hindlimb paralysis	THC	(Raman et al., 2004)
	hTDP-43	Footprint pattern analysis	Abnormal limb reflex (only visual description)	-	(Wils et al., 2010)
	hSOD^{G93A}	Open Field, Nerve conduction test	-	-	(Modol et al., 2014)
Genetic mice models	Spastic mice (*Spa*)	Only descriptive	Walk in short steps/tiptoe, interlock hind feet, lack facility in swimming	-	(Chai, 1961)
	Spastic mice (*Spa*)	EMG recording of flexor muscle of the proximal hindlimb and forelimb	Rapid limb/tail tremor, toe-walking gait, lack of flexibility of trunk movements, difficulty in regaining upright posture	-	(Heller and Hallett, 1982)
	Spastic mice (*Spa*)	EMG of the hindlimbs	-	Diazepam, flunitrazepam, phenobarbitone, diphenylhydantoin, bromocriptine, baclofen, benztropine, sodium valproate	(Biscoe and Fry, 1982)
	Sepp $^{-/-}$	Neuroscore, Stride pattern analysis, Rotarod, Pole climb	shorter short stride pattern, decreased pole climb score, and rotarod when fed with selenium-deficient diet	-	(Hill et al., 2004)
Spinal Cord Injury (SCI)	Slc12a5$^{+/-}$	RDD (H-reflex)	-	-	(Boulenguez et al., 2010)
	CD-1	Spinal to sciatic direct current stimulation, Stretch-induced	-	-	(Ahmed, 2014)

		nerve/muscle response, H-reflex, Cortically evoked potentials, Sciatic nerve excitability			
	C57BL/6	-		Injection of botulinum toxin in the ipsilateral hamstring	(Salga et al., 2019)
	C57BL/6	EMG in the ventral part of the tail	-	-	(Bellardita et al., 2017)
	CD-1	RDD (H-reflex), Dorsal root potential, Ground locomotion test, Ladder-wheel	Changes of the peak paw area to the contralateral paw	Repeated anodal trans-spinal direct current stimulation (a-tsDCS)	(Mekhael et al., 2019)
	Vglut2^{Cre}, VIATT ^{Cre}, HoxB8^{Cre}, Cacna1d-eGFP^{Flex}	EMG of the ventral part of the tail	-	Nimodipine (FDA-approved L-type calcium channel blocker)	(Marcantoni et al., 2020)

Abbreviations: EAE (Experimental Autoimmune Encephalomyelitis), CBD (Cannabidiol), RDD (Rate-dependent depression), THC (Δ^9-tetrahydro-cannabinol)

References

Vignaud, A., Rivares, C., Noort, W., Koopmans, B., Loos, M., Jaspers, R.T., Kalinichev, M., 2019. Characterization of the motor phenotype and striatal muscle analysis in a mouse model of hereditary spasticity [abstract]. Mov. Disord. 34 (supply 2).

Adams, M.M., Hicks, A.L., 2005. Spasticity after spinal cord injury. Spinal Cord 43, 577-586.

Ahmed, Z., 2014. Trans-spinal direct current stimulation alters muscle tone in mice with and without spinal cord injury with spasticity. J Neurosci 34, 1701-1709.

Akay, T., Tourtellotte, W.G., Arber, S., Jessell, T.M., 2014. Degradation of mouse locomotor pattern in the absence of proprioceptive sensory feedback. P Natl Acad Sci USA 111, 16877-16882.

Akpinar, P., Atici, A., Ozkan, F.U., Aktas, I., Kulcu, D.G., Sari, A., Durmus, B., 2017. Reliability of the Modified Ashworth Scale and Modified Tardieu Scale in patients with spinal cord injuries. Spinal Cord 55, 944-949.

Al-Ghezi, Z.Z., Miranda, K., Nagarkatti, M., Nagarkatti, P.S., 2019. Combination of Cannabinoids, Delta9-Tetrahydrocannabinol and Cannabidiol, Ameliorates Experimental Multiple Sclerosis by Suppressing Neuroinflammation Through Regulation of miRNA-Mediated Signaling Pathways. Front Immunol 10, 1921.

Allison, S.C., Abraham, L.D., Petersen, C.L., 1996. Reliability of the Modified Ashworth Scale in the assessment of plantarflexor muscle spasticity in patients with traumatic brain injury. Int J Rehabil Res 19, 67-78.

Andresen, S.R., Biering-Sorensen, F., Hagen, E.M., Nielsen, J.F., Bach, F.W., Finnerup, N.B., 2016. Pain, spasticity and quality of life in individuals with traumatic spinal cord injury in Denmark. Spinal Cord 54, 973-979.

Armand, J., Kuypers, H.G., 1980. Cells of origin of crossed and uncrossed corticospinal fibers in the cat: a quantitative horseradish peroxidase study. Exp Brain Res 40, 23-34.

Arthur, K.C., Calvo, A., Price, T.R., Geiger, J.T., Chio, A., Traynor, B.J., 2016. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun 7, 12408.

Baker, D., Pryce, G., Croxford, J.L., Brown, P., Pertwee, R.G., Huffman, J.W., Layward, L., 2000. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 404, 84-87.

Bakheit, A.M., Maynard, V.A., Curnow, J., Hudson, N., Kodapala, S., 2003. The relation between Ashworth scale scores and the excitability of the alpha motor neurones in patients with post-stroke muscle spasticity. J Neurol Neurosurg Psychiatry 74, 646-648.

Balci, B.P., 2018. Spasticity Measurement. Noro Psikiyatr Ars 55, S49-S53.

Basso, D.M., Fisher, L.C., Anderson, A.J., Jakeman, L.B., McTigue, D.M., Popovich, P.G., 2006. Basso Mouse Scale for locomotion detects differences in recovery after spinal cord injury in five common mouse strains. J Neurotrauma 23, 635-659.

Becker, C.M., Hermans-Borgmeyer, I., Schmitt, B., Betz, H., 1986. The glycine receptor deficiency of the mutant mouse spastic: evidence for normal glycine receptor structure and localization. J Neurosci 6, 1358-1364.
Bellardita, C., Caggiano, V., Leiras, R., Caldeira, V., Fuchs, A., Bouvier, J., Low, P., Kiehn, O., 2017. Spatiotemporal correlation of spinal network dynamics underlying spasms in chronic spinalized mice. Elife 6.
Belloli, S., Zanotti, L., Murtaj, V., Mazzon, C., Di Grigoli, G., Monterisi, C., Masiello, V., Iaccarino, L., Cappelli, A., Poliani, P.L., Politi, L.S., Moresco, R.M., 2018. (18)F-VC701-PET and MRI in the in vivo neuroinflammation assessment of a mouse model of multiple sclerosis. J Neuroinflammation 15, 33.
Bennett, D.J., Gorassini, M., Fouad, K., Sanelli, L., Han, Y., Cheng, J., 1999. Spasticity in rats with sacral spinal cord injury. J Neurotrauma 16, 69-84.
Bennett, D.J., Sanelli, L., Cooke, C.L., Harvey, P.J., Gorassini, M.A., 2004. Spastic long-lasting reflexes in the awake rat after sacral spinal cord injury. J Neurophysiol 91, 2247-2258.
Bergamaschi, M.M., Queiroz, R.H., Zuardi, A.W., Crippa, J.A., 2011. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf 6, 237-249.
Biscoe, T.J., Duchen, M.R., 1986. Synaptic physiology of spinal motoneurones of normal and spastic mice: an in vitro study. J Physiol 379, 275-292.
Biscoe, T.J., Fry, J.P., 1982. Some pharmacological studies on the spastic mouse. Br J Pharmacol 75, 23-35.
Biscoe, T.J., Fry, J.P., Rickets, C., 1984. Changes in benzodiazepine receptor binding as seen autoradiographically in the central nervous system of the spastic mouse. J Physiol 352, 509-516.
Borthwick, G.M., Taylor, R.W., Walls, T.J., Tonska, K., Taylor, G.A., Shaw, P.J., Ince, P.G., Turnbull, D.M., 2006. Motor neuron disease in a patient with a mitochondrial tRNAIle mutation. Ann Neurol 59, 570-574.
Boulenguez, P., Liabeuf, S., Bos, R., Bras, H., Jean-Xavier, C., Brocard, C., Stil, A., Darbon, P., Cattaert, D., Delpire, E., Marsala, M., Vinay, L., 2010. Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. Nat Med 16, 302-307.
Brown, A., Weaver, L.C., 2012. The dark side of neuroplasticity. Exp Neurol 235, 133-141.
Bucy, P.C., Keplinger, J.E., Siqueira, E.B., 1964. Destruction of the "Pyramidal Tract" in Man. J Neurosurg 21, 285-298.
Burke, D., Wissel, J., Donnan, G.A., 2013. Pathophysiology of spasticity in stroke. Neurology 80, S20-26.
Burridge, J.H., Wood, D.E., Hermens, H.J., Voerman, G.E., Johnson, G.R., van Wijck, F., Platz, T., Gregoric, M., Hitchcock, R., Pandyan, A.D., 2005. Theoretical and methodological considerations in the measurement of spasticity. Disabil Rehabil 27, 69-80.
Burrows, D.J., McGown, A., Jain, S.A., De Felice, M., Ramesh, T.M., Sharrack, B., Majid, A., 2019. Animal models of multiple sclerosis: From rodents to zebrafish. Mult Scler 25, 306-324.
Carmel, J.B., Martin, J.H., 2014. Motor cortex electrical stimulation augments sprouting of the corticospinal tract and promotes recovery of motor function. Front Integr Neurosci 8, 51.
Carp, J.S., Tennissen, A.M., Chen, X.Y., Schalk, G., Wolpaw, J.R., 2005. Long-term spinal reflex studies in awake behaving mice. J Neurosci Methods 149, 134-143.
Chai, C.K., 1961. Hereditary spasticity in mice. Journal of Heredity 52, 241-243.
Chamma, I., Chevy, Q., Poncer, J.C., Levi, S., 2012. Role of the neuronal K-Cl co-transporter KCC2 in inhibitory and excitatory neurotransmission. Front Cell Neurosci 6, 5.
Chia, R., Chio, A., Traynor, B.J., 2018. Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. Lancet Neurol 17, 94-102.
Chio, A., Calvo, A., Moglia, C., Gamna, F., Mattei, A., Mazzini, L., Mora, G., Parals, 2012. Non-invasive ventilation in amyotrophic lateral sclerosis: a 10 year population based study. J Neurol Neurosurg Psychiatry 83, 377-381.
Chio, A., Calvo, A., Moglia, C., Mazzini, L., Mora, G., group, P.s., 2011a. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry 82, 740-746.
Chio, A., Canosa, A., Gallo, S., Cammarosano, S., Moglia, C., Fuda, G., Calvo, A., Mora, G., group, P., 2011b. ALS clinical trials: do enrolled patients accurately represent the ALS population? Neurology 77, 1432-1437.
Collmann, F.M., Pijnenburg, R., Hamzei-Taj, S., Minassian, A., Folz-Donahue, K., Kukat, C., Aswendt, M., Hoehn, M., 2019. Individual in vivo Profiles of Microglia Polarization After Stroke, Represented by the Genes iNOS and Ym1. Front Immunol 10, 1236.
Coull, J.A., Boudreau, D., Bachand, K., Prescott, S.A., Nault, F., Sik, A., De Koninck, P., De Koninck, Y., 2003. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. Nature 424, 938-942.
D'Amico, J.M., Condliffe, E.G., Martins, K.J., Bennett, D.J., Gorassini, M.A., 2014. Recovery of neuronal and network excitability after spinal cord injury and implications for spasticity. Front Integr Neurosci 8, 36.
Delwaide, P.J., Oliver, E., 1988. Short-latency autogenic inhibition (IB inhibition) in human spasticity. J Neurol Neurosurg Psychiatry 51, 1546-1550.
Dietz, V., 2008. Spasticity-spastic movement disorder. Spinal Cord 46, 588.

Elbasiouny, S.M., Moroz, D., Bakr, M.M., Mushahwar, V.K., 2010. Management of spasticity after spinal cord injury: current techniques and future directions. Neurorehabil Neural Repair 24, 23-33.
Elmore, M.R., Najafi, A.R., Koike, M.A., Dagher, N.N., Spangenberg, E.E., Rice, R.A., Kitazawa, M., Matusow, B., Nguyen, H., West, B.L., Green, K.N., 2014. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. Neuron 82, 380-397.
Emos, M.C., Agarwal, S., 2020. Neuroanatomy, Upper Motor Neuron Lesion, StatPearls, Treasure Island (FL).
Fink, J.K., 2013. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol 126, 307-328.
Finnerup, N.B., 2017. Neuropathic pain and spasticity: intricate consequences of spinal cord injury. Spinal Cord 55, 1046-1050.
Fleuren, J.F., Voerman, G.E., Erren-Wolters, C.V., Snoek, G.J., Rietman, J.S., Hermens, H.J., Nene, A.V., 2010. Stop using the Ashworth Scale for the assessment of spasticity. J Neurol Neurosurg Psychiatry 81, 46-52.
Fuchs, A., Ringer, C., Bilkei-Gorzo, A., Weihe, E., Roeper, J., Schutz, B., 2010. Downregulation of the potassium chloride cotransporter KCC2 in vulnerable motoneurons in the SOD1-G93A mouse model of amyotrophic lateral sclerosis. J Neuropathol Exp Neurol 69, 1057-1070.
Ganapathy, V., Graham, G.D., DiBonaventura, M.D., Gillard, P.J., Goren, A., Zorowitz, R.D., 2015. Caregiver burden, productivity loss, and indirect costs associated with caring for patients with poststroke spasticity. Clin Interv Aging 10, 1793-1802.
Genc, B., Gozutok, O., Ozdinler, P.H., 2019. Complexity of Generating Mouse Models to Study the Upper Motor Neurons: Let Us Shift Focus from Mice to Neurons. Int J Mol Sci 20.
Ghareghani, M., Scavo, L., Arnoult, D., Zibara, K., Farhadi, N., 2018a. Melatonin therapy reduces the risk of osteoporosis and normalizes bone formation in multiple sclerosis. Fundam Clin Pharmacol 32, 181-187.
Ghareghani, M., Zibara, K., Sadeghi, H., Farhadi, N., 2018b. Spasticity Treatment Ameliorates the Efficacy of Melatonin Therapy in Experimental Autoimmune Encephalomyelitis (EAE) Mouse Model of Multiple Sclerosis. Cell Mol Neurobiol 38, 1145-1151.
Gill, C., Phelan, J.P., Hatzipetros, T., Kidd, J.D., Tassinari, V.R., Levine, B., Wang, M.Z., Moreno, A., Thompson, K., Maier, M., Grimm, J., Gill, A., Vieira, F.G., 2019. SOD1-positive aggregate accumulation in the CNS predicts slower disease progression and increased longevity in a mutant SOD1 mouse model of ALS. Sci Rep 9, 6724.
Graham, L.A., 2013. Management of spasticity revisited. Age Ageing 42, 435-441.
Gras, M., Leclercq, C., 2017. Spasticity and hyperselective neurectomy in the upper limb. Hand Surg Rehabil 36, 391-401.
Gu, Z., Kalambogias, J., Yoshioka, S., Han, W., Li, Z., Kawasawa, Y.I., Pochareddy, S., Li, Z., Liu, F., Xu, X., Wijeratne, H.R.S., Ueno, M., Blatz, E., Salomone, J., Kumanogoh, A., Rasin, M.R., Gebelein, B., Weirauch, M.T., Sestan, N., Martin, J.H., Yoshida, Y., 2017. Control of species-dependent cortico-motoneuronal connections underlying manual dexterity. Science 357, 400-404.
Haas, B.M., Bergstrom, E., Jamous, A., Bennie, A., 1996. The inter rater reliability of the original and of the modified Ashworth scale for the assessment of spasticity in patients with spinal cord injury. Spinal Cord 34, 560-564.
Haugh, A.B., Pandyan, A.D., Johnson, G.R., 2006. A systematic review of the Tardieu Scale for the measurement of spasticity. Disabil Rehabil 28, 899-907.
Heetla, H.W., Staal, M.J., Proost, J.H., van Laar, T., 2014. Clinical relevance of pharmacological and physiological data in intrathecal baclofen therapy. Arch Phys Med Rehabil 95, 2199-2206.
Heller, A.H., Hallett, M., 1982. Electrophysiological studies with the spastic mutant mouse. Brain Res 234, 299-308.
Hill, K.E., Zhou, J., McMahan, W.J., Motley, A.K., Atkins, J.F., Gesteland, R.F., Burk, R.F., 2003. Deletion of selenoprotein P alters distribution of selenium in the mouse. J Biol Chem 278, 13640-13646.
Hill, K.E., Zhou, J., McMahan, W.J., Motley, A.K., Burk, R.F., 2004. Neurological dysfunction occurs in mice with targeted deletion of the selenoprotein P gene. J Nutr 134, 157-161.
Hinderer, S.R., Dixon, K., 2001. Physiologic and clinical monitoring of spastic hypertonia. Phys Med Rehabil Clin N Am 12, 733-746.
Hodgetts, S.I., Plant, G.W., Harvey, A.R., 2009. Chapter 14 - Spinal Cord Injury: experimental animal models and relation to human therapy, in: Watson, C., Paxinos, G., Kayalioglu, G. (Eds.), The Spinal Cord. Academic Press, San Diego, pp. 209-237.
Hoffmann, P., 1910. Beiträge zur Kenntnis der menschlichen Reflexe mit besonderer Berücksichtigung der elektrischen Erscheinung. Arch Anat Physiol 1, 223-246.
Hoffmann, P., 1918. Über die Beziehung der Sehnenreflexe zur willkürlichen Bewegung zum Tonus. Z Biol 68, 351-370.

Hughes, C., Howard, I.M., 2013. Spasticity management in multiple sclerosis. Phys Med Rehabil Clin N Am 24, 593-604.
Hultborn, H., Nielsen, J.B., 1996. Comments: methodological problems of comparing F responses and H reflexes. Muscle Nerve 19, 1347-1348.
Iglesias, C., Sangari, S., El Mendili, M.M., Benali, H., Marchand-Pauvert, V., Pradat, P.F., 2015. Electrophysiological and spinal imaging evidences for sensory dysfunction in amyotrophic lateral sclerosis. BMJ Open 5, e007659.
Jaenisch, N., Witte, O.W., Frahm, C., 2010. Downregulation of potassium chloride cotransporter KCC2 after transient focal cerebral ischemia. Stroke 41, e151-159.
Jang, S.H., 2014. The corticospinal tract from the viewpoint of brain rehabilitation. J Rehabil Med 46, 193-199.
Joosten, E.A., Schuitman, R.L., Vermelis, M.E., Dederen, P.J., 1992. Postnatal development of the ipsilateral corticospinal component in rat spinal cord: a light and electron microscopic anterograde HRP study. J Comp Neurol 326, 133-146.
Justice, J.N., Carter, C.S., Beck, H.J., Gioscia-Ryan, R.A., McQueen, M., Enoka, R.M., Seals, D.R., 2014. Battery of behavioral tests in mice that models age-associated changes in human motor function. Age (Dordr) 36, 583-592.
Kakinohana, O., Hefferan, M.P., Nakamura, S., Kakinohana, M., Galik, J., Tomori, Z., Marsala, J., Yaksh, T.L., Marsala, M., 2006. Development of GABA-sensitive spasticity and rigidity in rats after transient spinal cord ischemia: a qualitative and quantitative electrophysiological and histopathological study. Neuroscience 141, 1569-1583.
Karbasforoushan, H., Cohen-Adad, J., Dewald, J.P.A., 2019. Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. Nat Commun 10, 3524.
Kheder, A., Nair, K.P., 2012. Spasticity: pathophysiology, evaluation and management. Pract Neurol 12, 289-298.
Ksiazek-Winiarek, D.J., Szpakowski, P., Glabinski, A., 2015. Neural Plasticity in Multiple Sclerosis: The Functional and Molecular Background. Neural Plasticity 2015.
Lamy, J.C., Wargon, I., Mazevet, D., Ghanim, Z., Pradat-Diehl, P., Katz, R., 2009. Impaired efficacy of spinal presynaptic mechanisms in spastic stroke patients. Brain 132, 734-748.
Lance, J.W., 1990. What is spasticity? Lancet 335, 606.
Lang, C., Bradley, P.M., Jacobi, A., Kerschensteiner, M., Bareyre, F.M., 2013. STAT3 promotes corticospinal remodelling and functional recovery after spinal cord injury. EMBO Rep 14, 931-937.
Lee, S., Toda, T., Kiyama, H., Yamashita, T., 2014. Weakened rate-dependent depression of Hoffmann's reflex and increased motoneuron hyperactivity after motor cortical infarction in mice. Cell Death Dis 5, e1007.
Lemon, R.N., 2008. Descending pathways in motor control. Annu Rev Neurosci 31, 195-218.
Lemon, R.N., 2010. What drives corticospinal output? F1000 Biology Reports 2.
Leo, A., Naro, A., Molonia, F., Tomasello, P., Sacca, I., Bramanti, A., Russo, M., Bramanti, P., Quartarone, A., Calabro, R.S., 2017. Spasticity Management: The Current State of Transcranial Neuromodulation. PM R 9, 1020-1029.
Li, S., 2017. Spasticity, Motor Recovery, and Neural Plasticity after Stroke. Frontiers in Neurology 8.
Li, S., Chen, Y.T., Francisco, G.E., Zhou, P., Rymer, W.Z., 2019. A Unifying Pathophysiological Account for Post-stroke Spasticity and Disordered Motor Control. Front Neurol 10, 468.
Li, S., Francisco, G.E., 2015. New insights into the pathophysiology of post-stroke spasticity. Front Hum Neurosci 9, 192.
Liske, H., Qian, X., Anikeeva, P., Deisseroth, K., Delp, S., 2013. Optical control of neuronal excitation and inhibition using a single opsin protein, ChR2. Sci Rep 3, 3110.
Lundstrom, E., Smits, A., Terent, A., Borg, J., 2010. Time-course and determinants of spasticity during the first six months following first-ever stroke. J Rehabil Med 42, 296-301.
Lundstrom, E., Terent, A., Borg, J., 2008. Prevalence of disabling spasticity 1 year after first-ever stroke. Eur J Neurol 15, 533-539.
Lundy-Ekmann, L., 2002. Neuroscience: Fundamentals for Rehabiliation.
Magladery, J.W., Mc, D.D., Jr., 1950. Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibers. Bull Johns Hopkins Hosp 86, 265-290.
Malhotra, S., Cousins, E., Ward, A., Day, C., Jones, P., Roffe, C., Pandyan, A., 2008. An investigation into the agreement between clinical, biomechanical and neurophysiological measures of spasticity. Clin Rehabil 22, 1105-1115.
Marcantoni, M., Fuchs, A., Low, P., Bartsch, D., Kiehn, O., Bellardita, C., 2020. Early delivery and prolonged treatment with nimodipine prevents the development of spasticity after spinal cord injury in mice. Sci Transl Med 12.
Matthews, W.B., 1966. Ratio of maximum H reflex to maximum M response as a measure of spasticity. J Neurol Neurosurg Psychiatry 29, 201-204.

Mayer, N.H., 1997. Clinicophysiologic concepts of spasticity and motor dysfunction in adults with an upper motoneuron lesion. Muscle Nerve Suppl 6, S1-13.
Mazzocchio, R., Rossi, A., 1997. Involvement of spinal recurrent inhibition in spasticity. Further insight into the regulation of Renshaw cell activity. Brain 120 (Pt 6), 991-1003.
McCarthy, D.P., Richards, M.H., Miller, S.D., 2012. Mouse models of multiple sclerosis: experimental autoimmune encephalomyelitis and Theiler's virus-induced demyelinating disease. Methods Mol Biol 900, 381-401.
Mekhael, W., Begum, S., Samaddar, S., Hassan, M., Toruno, P., Ahmed, M., Gorin, A., Maisano, M., Ayad, M., Ahmed, Z., 2019. Repeated anodal trans-spinal direct current stimulation results in long-term reduction of spasticity in mice with spinal cord injury. J Physiol 597, 2201-2223.
Meseguer-Henarejos, A.B., Sanchez-Meca, J., Lopez-Pina, J.A., Carles-Hernandez, R., 2018. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. Eur J Phys Rehabil Med 54, 576-590.
Mitchell, J., Paul, P., Chen, H.J., Morris, A., Payling, M., Falchi, M., Habgood, J., Panoutsou, S., Winkler, S., Tisato, V., Hajitou, A., Smith, B., Vance, C., Shaw, C., Mazarakis, N.D., de Belleroche, J., 2010. Familial amyotrophic lateral sclerosis is associated with a mutation in D-amino acid oxidase. Proc Natl Acad Sci U S A 107, 7556-7561.
Modol, L., Mancuso, R., Ale, A., Francos-Quijorna, I., Navarro, X., 2014. Differential effects on KCC2 expression and spasticity of ALS and traumatic injuries to motoneurons. Front Cell Neurosci 8, 7.
Moreno-Lopez, Y., Olivares-Moreno, R., Cordero-Erausquin, M., Rojas-Piloni, G., 2016. Sensorimotor Integration by Corticospinal System. Front Neuroanat 10, 24.
Moritz, C.T., 2018. Now is the Critical Time for Engineered Neuroplasticity. Neurotherapeutics 15, 628-634.
Mukherjee, A., Chakravarty, A., 2010. Spasticity mechanisms - for the clinician. Front Neurol 1, 149.
O'Reilly, M.L., Tom, V.J., 2020. Neuroimmune System as a Driving Force for Plasticity Following CNS Injury. Frontiers in Cellular Neuroscience 14.
Opheim, A., Danielsson, A., Alt Murphy, M., Persson, H.C., Sunnerhagen, K.S., 2014. Upper-limb spasticity during the first year after stroke: stroke arm longitudinal study at the University of Gothenburg. Am J Phys Med Rehabil 93, 884-896.
Oudega, M., Perez, M.A., 2012. Corticospinal reorganization after spinal cord injury. J Physiol 590, 3647-3663.
Pandyan, A.D., Johnson, G.R., Price, C.I., Curless, R.H., Barnes, M.P., Rodgers, H., 1999. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. Clin Rehabil 13, 373-383.
Patejdl, R., Zettl, U.K., 2017. Spasticity in multiple sclerosis: Contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions. Autoimmun Rev 16, 925-936.
Pearson-Stuttard, J., Guzman-Castillo, M., Penalvo, J.L., Rehm, C.D., Afshin, A., Danaei, G., Kypridemos, C., Gaziano, T., Mozaffarian, D., Capewell, S., O'Flaherty, M., 2016. Modeling Future Cardiovascular Disease Mortality in the United States: National Trends and Racial and Ethnic Disparities. Circulation 133, 967-978.
Penn, R.D., Savoy, S.M., Corcos, D., Latash, M., Gottlieb, G., Parke, B., Kroin, J.S., 1989. Intrathecal baclofen for severe spinal spasticity. N Engl J Med 320, 1517-1521.
Philips, T., Rothstein, J.D., 2015. Rodent Models of Amyotrophic Lateral Sclerosis. Curr Protoc Pharmacol 69, 5 67 61-65 67 21.
Picelli, A., Tamburin, S., Gajofatto, F., Zanette, G., Praitano, M., Saltuari, L., Corradini, C., Smania, N., 2014. Association between severe upper limb spasticity and brain lesion location in stroke patients. Biomed Res Int 2014, 162754.
Pryce, G., Baker, D., 2007. Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors. Br J Pharmacol 150, 519-525.
Raman, C., McAllister, S.D., Rizvi, G., Patel, S.G., Moore, D.H., Abood, M.E., 2004. Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. Amyotroph Lateral Scler Other Motor Neuron Disord 5, 33-39.
Renaud, L., Picher-Martel, V., Codron, P., Julien, J.P., 2019. Key role of UBQLN2 in pathogenesis of amyotrophic lateral sclerosis and frontotemporal dementia. Acta Neuropathol Commun 7, 103.
Ritz, L.A., Friedman, R.M., Rhoton, E.L., Sparkes, M.L., Vierck, C.J., Jr., 1992. Lesions of cat sacrocaudal spinal cord: a minimally disruptive model of injury. J Neurotrauma 9, 219-230.
Robberecht, W., 2000. Oxidative stress in amyotrophic lateral sclerosis. J Neurol 247 Suppl 1, I1-6.
Robinson, A.P., Harp, C.T., Noronha, A., Miller, S.D., 2014. The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. Handb Clin Neurol 122, 173-189.
Rosenzweig, E.S., Brock, J.H., Culbertson, M.D., Lu, P., Moseanko, R., Edgerton, V.R., Havton, L.A., Tuszynski, M.H., 2009. Extensive spinal decussation and bilateral termination of cervical corticospinal projections in rhesus monkeys. J Comp Neurol 513, 151-163.

Rudroff, T., Sosnoff, J., 2018. Cannabidiol to Improve Mobility in People with Multiple Sclerosis. Frontiers in Neurology 9.
Ryu, Y., Ogata, T., Nagao, M., Kitamura, T., Morioka, K., Ichihara, Y., Doi, T., Sawada, Y., Akai, M., Nishimura, R., Fujita, N., 2017. The swimming test is effective for evaluating spasticity after contusive spinal cord injury. PLoS One 12, e0171937.
Salga, M., Tseng, H.W., Alexander, K.A., Jose, B., Vaquette, C., Debaud, C., Gatin, L., Genet, F., Levesque, J.P., 2019. Blocking neuromuscular junctions with botulinum toxin A injection enhances neurological heterotopic ossification development after spinal cord injury in mice. Ann Phys Rehabil Med 62, 189-192.
Sangari, S., Perez, M.A., 2019. Imbalanced Corticospinal and Reticulospinal Contributions to Spasticity in Humans with Spinal Cord Injury. J Neurosci 39, 7872-7881.
Satoru Kai , K.N., 2013. Evoked EMG Makes Measurement of Muscle Tone Possible by Analysis of the H/M Ratio. Electrodiagnosis in New Frontiers of Clinical Research.
Schomburg, L., Schweizer, U., Holtmann, B., Flohe, L., Sendtner, M., Kohrle, J., 2003. Gene disruption discloses role of selenoprotein P in selenium delivery to target tissues. Biochem J 370, 397-402.
Sehgal, N., McGuire, J.R., 1998. Beyond Ashworth. Electrophysiologic quantification of spasticity. Phys Med Rehabil Clin N Am 9, 949-979, ix.
Sheean, D.G., 2009. Is spasticity painful? Eur J Neurol 16, 157-158.
Shelton, F.D., Volpe, B.T., Reding, M., 2001. Motor impairment as a predictor of functional recovery and guide to rehabilitation treatment after stroke. Neurorehabil Neural Repair 15, 229-237.
Sherrington, C.S., 1898. Decerebrate Rigidity, and Reflex Coordination of Movements. J Physiol 22, 319-332.
Simpson, D.M., Patel, A.T., Alfaro, A., Ayyoub, Z., Charles, D., Dashtipour, K., Esquenazi, A., Graham, G.D., McGuire, J.R., Odderson, I., 2017. OnabotulinumtoxinA Injection for Poststroke Upper-Limb Spasticity: Guidance for Early Injectors From a Delphi Panel Process. PM R 9, 136-148.
Sist, B., Fouad, K., Winship, I.R., 2014. Plasticity beyond peri-infarct cortex: spinal up regulation of structural plasticity, neurotrophins, and inflammatory cytokines during recovery from cortical stroke. Exp Neurol 252, 47-56.
Stevenson, V.L., Gras, A., Bardos, J.I., Broughton, J., 2015. The high cost of spasticity in multiple sclerosis to individuals and society. Mult Scler 21, 1583-1592.
Sunnerhagen, K.S., 2016. Predictors of Spasticity After Stroke. Curr Phys Med Rehabil Rep 4, 182-185.
Svensson, J., Borg, S., Nilsson, P., 2014. Costs and quality of life in multiple sclerosis patients with spasticity. Acta Neurol Scand 129, 13-20.
Tan, A.M., Chakrabarty, S., Kimura, H., Martin, J.H., 2012. Selective corticospinal tract injury in the rat induces primary afferent fiber sprouting in the spinal cord and hyperreflexia. J Neurosci 32, 12896-12908.
Toda, T., Ishida, K., Kiyama, H., Yamashita, T., Lee, S., 2014. Down-regulation of KCC2 expression and phosphorylation in motoneurons, and increases the number of in primary afferent projections to motoneurons in mice with post-stroke spasticity. PLoS One 9, e114328.
Tohyama, T., Kinoshita, M., Kobayashi, K., Isa, K., Watanabe, D., Kobayashi, K., Liu, M., Isa, T., 2017. Contribution of propriospinal neurons to recovery of hand dexterity after corticospinal tract lesions in monkeys. Proc Natl Acad Sci U S A 114, 604-609.
Trompetto, C., Marinelli, L., Mori, L., Pelosin, E., Curra, A., Molfetta, L., Abbruzzese, G., 2014. Pathophysiology of spasticity: implications for neurorehabilitation. Biomed Res Int 2014, 354906.
Wahl, A.S., Buchler, U., Brandli, A., Brattoli, B., Musall, S., Kasper, H., Ineichen, B.V., Helmchen, F., Ommer, B., Schwab, M.E., 2017. Optogenetically stimulating intact rat corticospinal tract post-stroke restores motor control through regionalized functional circuit formation. Nat Commun 8, 1187.
Wahl, A.S., Schwab, M.E., 2014. Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment. Front Hum Neurosci 8, 381.
Ward, A.B., 2012. A literature review of the pathophysiology and onset of post-stroke spasticity. Eur J Neurol 19, 21-27.
Ward, A.B., Aguilar, M., De Beyl, Z., Gedin, S., Kanovsky, P., Molteni, F., Wissel, J., Yakovleff, A., 2003. Use of botulinum toxin type A in management of adult spasticity--a European consensus statement. J Rehabil Med 35, 98-99.
Warsi, N.M., Tailor, J., Coulter, I.C., Shakil, H., Workewych, A., Haldenby, R., Breitbart, S., Strantzas, S., Vandenberk, M., Dewan, M.C., Ibrahim, G.M., 2020. Selective dorsal rhizotomy: an illustrated review of operative techniques. J Neurosurg Pediatr, 1-8.
Watson, C., Harrison, M., 2012. The location of the major ascending and descending spinal cord tracts in all spinal cord segments in the mouse: actual and extrapolated. Anat Rec (Hoboken) 295, 1692-1697.
Welniarz, Q., Dusart, I., Roze, E., 2017. The corticospinal tract: Evolution, development, and human disorders. Dev Neurobiol 77, 810-829.

Weydt, P., Hong, S., Witting, A., Moller, T., Stella, N., Kliot, M., 2005. Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival. Amyotroph Lateral Scler Other Motor Neuron Disord 6, 182-184.
White, W.F., Heller, A.H., 1982. Glycine receptor alteration in the mutant mouse spastic. Nature 298, 655-657.
Wils, H., Kleinberger, G., Janssens, J., Pereson, S., Joris, G., Cuijt, I., Smits, V., Ceuterick-de Groote, C., Van Broeckhoven, C., Kumar-Singh, S., 2010. TDP-43 transgenic mice develop spastic paralysis and neuronal inclusions characteristic of ALS and frontotemporal lobar degeneration. Proc Natl Acad Sci U S A 107, 3858-3863.
Yamanaka, K., Miller, T.M., McAlonis-Downes, M., Chun, S.J., Cleveland, D.W., 2006. Progressive spinal axonal degeneration and slowness in ALS2-deficient mice. Ann Neurol 60, 95-104.
Zhang, N., Fang, M., Chen, H., Gou, F., Ding, M., 2014. Evaluation of spinal cord injury animal models. Neural Regen Res 9, 2008-2012.
Ziv, I., Blackburn, N., Rang, M., Koreska, J., 1984. Muscle growth in normal and spastic mice. Dev Med Child Neurol 26, 94-99.