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Review

Brain regions and genes affecting limb-clasping responses

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ABSTRACT

Adult rodents picked up by the tail and slowly descending towards a horizontal surface extend all four limbs in anticipation of contact. Mouse mutants with pathologies in various brain regions and the spinal cord display instead a flexion response, often characterized by paw-clasping and a bat-like posture. These phenotypes are observed in mice with lesions in cerebellum, basal ganglia, and neocortex, as well as transgenic models of Alzheimer's disease. The underlying mechanism appears to include cerebello-cortico-reticular and cortico-striato-pallido-reticular pathways, possibly triggered by changes in noradrenaline and serotonin transmission.

Contents

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1. Paw-clasping in normal mice

When adult rodents are picked up by the tail and slowly lowered towards a horizontal surface, they extend all four paws in anticipation of contact with the ground (Fig. 1a). This response may be triggered by either visual or tactile stimuli, the latter with the vibrissae or paw (Irwin, 1968). Visual stimuli are usually sufficient to initiate the placing response, but, in some cases, depending on genetic background and age, even normal mice extend their paws only at the moment they touch the ground, due to retinal deficiencies found in some strains and the debilitating effect of aging. This aspect has been insufficiently examined, since, to our knowledge, no report exits on the influence of the most commonly used mouse strains on the placing response and how this response alters with aging. In addition to sensory pathways, the placing reflex depends on spinal motor pathways responsible for moving fore- and hindlimbs.

The visual placing response in rodents can only appear after eye opening during the second postnatal week. However, the tactile placing response can be evaluated throughout the postnatal period. In normal mice, the limb-clasping response is progressively converted to extension prior to weaning (Takahashi et al., 2010). Thus, the neural pathways responsible for limb extension mature very quickly to the adult form. Instead of limb extension, limb flexion occurs in early developmental stages, sometimes with clasping of fore- or hindpaws, as seen in brain-lesioned mice (Fig. 1b), sometimes with all four limbs tucked towards the axial part of the body in a bat-like posture (Fig. 1 c), hindpaw clasping presented in the form of a video by Guyenet et al. (2010). These anomalies are distinct from the normal response of grasping a bar, testable as early as postnatal day 3, and impaired in the *Reln*^{rl} (*reeler*) cerebellar mutant on postnatal day 11 (Laviola et al., 2006).

Even in normal adult mice, paw-clasping may occur instead of limb extension. The often used C57BL/6 mouse has good visual acuity relative to many other mouse strains and usually displays the visual placing response. However, up to 10% of C57B6/SJL hybrids displayed hindlimb clasping, presumably as a consequence of "abnormal" genes on the SJL background (Lalonde et al., 2003). But no hindlimb clasping was observed in B6C3 hybrids, indicating that the C3H background possesses no abnormal gene of this kind (Lalonde et al., 2004, 2005a). In this ignored branch of research, a high throughput analysis of mouse genetics is needed, though easily feasible, since this response can be assessed even by relatively untrained technicians, information likely to be useful in screening neurological mutants.

The purpose of the present review is to summarize findings of mouse mutations affecting the placing reflex, regarding not only the functional effects of genes but also sensorimotor regions underlying normal and abnormal motor responses. Table 1 summarizes murine mutants with spinal and brain lesions exhibiting the abnormal paw-clasping response.

2. Spinal cord

Massive destruction of α-motoneurons prevents any possibility of responding. However, abnormal responses may occur in mice with ventral spinal damage prior to paralysis. This is the case in mice with the spontaneous *mnd* (motor neuron damage) mutation of the *Cln8*'gene, encoding ceroid-lipofuscinosis neuronal 8, eventually paralyzed as a result of α-motoneuron degeneration (Messer and Flaherty, 1986). Prior to paralysis, the *Cln8*^{mnd} mutants display limb flexion, perhaps due to dysfunction at the spinal level. But since *Cln8* mRNA is highly expressed in adult neocortex and other brain regions (Lonka et al., 2005), the abnormal phenotype may also be due to brain dysfunction, though neuropathologic analyses reveal mainly spinal damage.

A role for dysfunctional α-motoneurons in pathological reflexes is supported by observing hindpaw clasping and the bat-like posture in transgenic mice expressing full-length mutated *Ar* (androgen receptor), with α-motoneuron degeneration but without volumetric changes in cerebellum and striatum (McManamny et al., 2002), brain areas presumed to be involved in the same neurologic responses (see below). Moreover, hindpaw clasping provoked by contact with a glass surface, though not in the usual air suspension procedure, was observed in null mutants of *Smn2* (survival motoneuron type 2) with inserted human *SMN2* and *SMNdelta7* variants to prevent embryonic lethality and mitigate spinal and brainstem motoneuron loss (El-Khodor et al., 2008). Hindpaw clasping was also detected in the *NEFL*^{P22S} mutant model of Charcot-Marie-Tooth disease type 2E, mutated for neurofilament of light molecular weight and characterized by axonopathy of spinal pathways (Dequen et al., 2010). In addition, fore- and hindpaw clasping

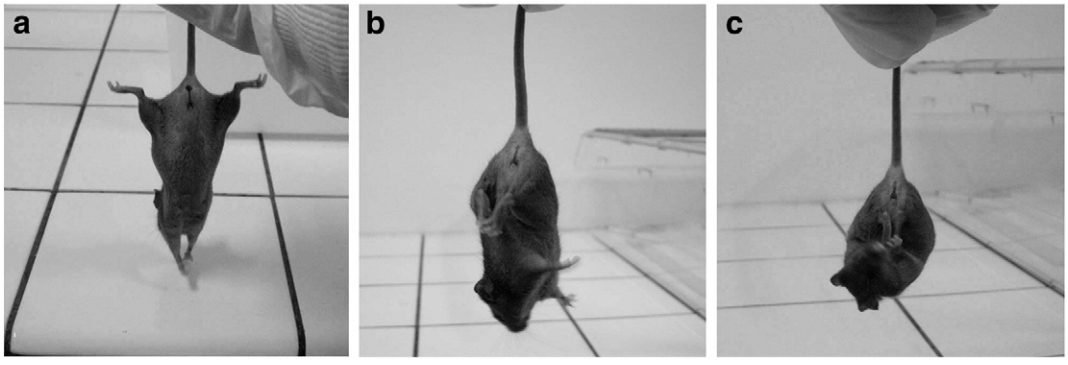

Fig. 1 – Limb extension in normal mice (a), whereas in *Dab1*^{scm} (*scrambler*) mutants with cell ectopias and degeneration in cerebellar cortex there is paw-clasping (b) and a bat-like posture (c).

Table 1 – Mutants with central nervous lesions exhibiting paw-clasping.

Mutant (name)	Mutation (type)	Pathology	References
Cln8^{mnd}	natural	α-motoneuron	Messer and Flaherty, 1986
Ar	transgenic	α-motoneuron	McManamny et al., 2002
Smn2 SMN2+ SMNdelta7	knockout and transgenic	α-motoneuron	El-Khodor et al., 2008
NEFL^{P22S}	transgenic	spinal cord axonopathy	Dequen et al., 2010
Hoxb8	knockout	dorsal spinal ganglia	Tsuchida et al., 1994 van den Akker et al., 1999
Dync1h1^{Cra1}	N-ethyl-N-nitrosoura-induced	dorsal spinal roots, striatum	Braunstein et al., 2010 Dupuis et al., 2009
Dst$^{dt\text{-}J}$	natural	dorsal spinal, spinocerebellar	Lalonde et al., 2005a
Girk2^{Wv}	natural	cerebellum, susbstantia nigra	Lalonde, 1987a
Rora^{sg}	natural	cerebellum	Lalonde, 1987b
Dab1^{scm}	natural	cerebellum, neocortex	herein
Cacna1a$^{tg\text{-}rol}$	natural	cerebellum	Takahashi et al., 2009, 2010
Cacna1a$^{tg\text{-}la}$	natural	cerebellum	Alonso et al., 2008
ATXN3/Q79	transgenic	cerebellum	Chou et al., 2008
ATXN3/Q84	transgenic	cerebellum	Cemal et al., 2002
ATXN7/Q52	transgenic	cerebellum	Chou et al., 2010
ATXN7/Q92	transgenic	cerebellum	Garden et al., 2002
Prkcc	transgenic	cerebellum	Zhang et al., 2009
Ccnd1	knockout	cerebellum	Sicinski et al., 1995
Rai1	knockout	cerebellum	Bi et al., 2007
dt	natural	cerebellum	Lorden et al., 1984
R6/1 R6/2	transgenic	striatum	Mangiarini et al., 1996
HDHQ89 *HDHQ48*	transgenic	striatum	Reddy et al., 1998
Hdh150	transgenic	striatum	Heng et al., 2007 Lin et al., 2001
Bdnf	conditional knockouts	fore- or hindbrain	Baquet et al., 2004, 2005 Rauskolb et al., 2010 Strand et al., 2007
Atg7	conditional knockout, transgenic	cerebellum, neocortex	Komatsu et al., 2006
Dicer1	conditional knockout	striatum	Cuellar et al., 2008
Foxb1	knockout	diencephalon, midbrain	Labosky et al., 1997
Hexa	knockout	sensorimotor cortex spinal cord	Miklyaeva et al., 2004
Mecp2	knockout		Santos et al., 2007
Cav1	knockout	brain	Trushina et al., 2006
Npr2	knockout	medulla	Tamura et al., 2004
Prp	transgenic	neocortex	Wang et al., 2009
APP_{751}SL+*PS1*/M233+L235P	knockin	brain, spinal cord	Wirths et al., 2007
APP_{751}SWE	transgenic	neocortex	Lalonde et al., 2005b
APP_{695}SWE	transgenic	neocortex	Lalonde et al., 2003

was reported in *Hoxb8* null mutants, the normal gene being expressed in ventral horn of the neural tube (Tsuchida et al., 1994; van den Akker et al., 1999). However, the main area of degeneration in *Hoxb8* knockouts occurs in spinal dorsal ganglia, indicating the possible influence of sensory pathways in the abnormal reflex.

A specific role of sensory pathways is supported by observing hindpaw clasping in mice with the *cramping 1* mutation of *Dync1h1*, encoding dynein cytoplasmic 1 heavy chain (Dupuis et al., 2009). *Dync1h1*^{Cra1} mutants have smaller dorsal roots, thinner sensory axons, and muscle spindle denervation without α-motoneuron loss. However, *Dync1h1*^{Cra1} mutants also have striatal atrophy (Braunstein et al., 2010), which may cause the same neurologic sign (see below). Nevertheless, the influence of dorsal sensory tracts in paw-clasping is supported by this response being exhibited by *Dst*$^{dt\text{-}J}$ (*dystonia musculorum*) mutants with white matter atrophy in this area (Lalonde et al., 2005a), but also in spinocerebellar pathways. Thus, spinal damage likely mediates the abnormal paw-clasping reflex through somatosensory and motor pathways, including the spinocerebellar projection.

3. Cerebellum

The pathological clasping reflex has been described in several murine mutations with cerebellar atrophy, including mice with the spontaneous semi-dominant *Weaver* mutation of *Girk2* (Lalonde, 1987a), encoding a G protein-related inward rectifying potassium channel (Patil et al., 1995). *Girk2*^{Wv} mutants are characterized by degenerated cerebellar granule and Purkinje cells (Herrup and Trenkner, 1987; Hirano and Dembitzer, 1973). The contribution of extracerebellar regions to behavior is possible in view of degenerating neurons found

in substantia nigra pars compacta of *Girk2*^{Wv} homozygotes, leading to reduced dopamine concentrations in dorsal striatum (Roffler-Tarlov and Graybiel, 1986; Roffler-Tarlov et al., 1996; Triarhou et al., 1988). However, *Rora*^{sg} mice with the spontaneous *staggerer* mutation of *Rora*, encoding retinoid-like orphan nuclei receptor α, also characterized by granule and Purkinje cell losses (Herrup, 1983; Herrup and Mullen, 1979) but with normal dopamine concentrations in dorsal striatum (Roffler-Tarlov and Graybiel, 1986), show the same clasping phenotype (Lalonde, 1987b), perhaps indicating that cerebellar damage alone causes this response. This hypothesis is supported by observing paw-clasping and the bat-like posture in the spontaneous autosomal recessive *Dab1*^{scm} (*scrambler*) mutation of disabled-1 (Fig. 1b and c), characterized by cell ectopias in cerebellar cortex, together with Purkinje and granule cell losses, though ectopias also occur in neocortex (Goldowitz et al., 1997; Sweet et al., 1996).

The contribution of the cerebellum in paw-clasping is further demonstrated by observing other ataxic mice with cerebellar atrophy, notably the spontaneous *Cacna1a*$^{tg\text{-}rol}$ (*rolling Nagoya*) mutation of a calcium channel at neonatal (Takahashi et al., 2010) and adult (Takahashi et al., 2009) stages, corresponding to the gene responsible for human spinocerebellar atrophy type 6 (SCA6), as well as transgenic models of other human spinocerebellar atrophies, namely *ATXN3*/Q79 (Chou et al., 2008) and *ATXN3*/Q84 (Cemal et al., 2002) for SCA3, *ATXN7*/Q52 (Chou et al., 2010) and *ATXN7*/Q92 (Garden et al., 2002) for SCA7.

Paw-clasping is even observed in mutants with cerebellar dysfunction without overt ataxia, notably in heterozygotes with the *leaner* mutation of the same gene responsible for *rolling Nagoya*, as ataxia is seen only in *Cacna1a*$^{tg\text{-}la}$ homozygotes (Alonso et al., 2008). The same phenotype of clasping without ataxia was reported in transgenic mice with a mutation of *Prkcc*, encoding protein kinase C-gamma (PKCγ), responsible for SCA14 (Zhang et al., 2009). Another gene predominantly expressed in the cerebellum (but also in striatum) and causing abnormal motor phenotypes is *RAI1*, encoding retinoic acid 1, primarity responsible for Smith–Magenis and Potocki–Lupsky syndromes, modifying as well the age of onset in SCA2 according to its CAG repeat length (Hayes et al., 2000). *Rai1* null mutants exhibit hindpaw clasping and the bat-like posture with deficits of motor coordination on the rotorod test but with no overt ataxia (Bi et al., 2007). Likewise, paw-clasping was observed in null mutants of *Ccnd1*, encoding cyclin D1 (Sicinski et al., 1995), characterized by reduced cerebellar size as a result of impaired proliferation of granule cell precursors (Pogoriler et al., 2006), though once again without ataxia.

The importance of cerebellar afferents on paw-clasping is indicated by observing this response not only in ataxic *Dst*$^{dt\text{-}J}$ mutants with spinocerebellar atrophy (Lalonde et al., 2005a) but also in non-ataxic *dt* (*dystonic*) mutant rats with no obvious cerebellar degeneration but with a cerebellum denervated of noradrenergic fibers (Lorden et al., 1984). These results point towards a possible role of noradrenaline in the clasping response. But it remains to be determined whether this response may be diminished or even elimimated by pharmacological manipulations of noradrenergic transmission in the cerebellum or elsewhere.

Thus, paw-clasping does not depend on the presence of ataxia in a cerebellar mutant. Conversely, the presence of ataxia in a cerebellar mutant does not guarantee paw-clasping, indicating a double dissociation between the two. This is revealed in the ataxic *Grid2*^{Lc} (*Lurcher*) mutant, with neurologic signs caused by a gain-in-malfunction of *Grid2*, encoding an ionotropic glutamate receptor (GluRδ2) predominantly expressed in Purkinje cells (Zuo et al., 1997). Like the ataxic *Rora*^{sg} mutant, the *Grid2*^{Lc} mutant has massive degeneration of cerebellar cortex (Caddy and Biscoe, 1979), and yet only the former clasps (Lalonde, 1987b; personal observations). In the *Grid2*^{Lc} mutant, the Purkinje cell loss is nearly total (Caddy and Biscoe, 1979), whereas in *Rora*^{sg} about 25% of these cells remain (Herrup, 1983; Herrup and Mullen, 1979). Despite ataxia, *Grid2*^{Lc} mutants have normal activity levels relative to non-ataxic mice of the same background strain (Lalonde et al., 1986), whereas ataxic *Rora*^{sg} mutants are hypoactive relative to their controls (Lalonde et al., 1988), leading to the conclusion that dysfunctional Purkinje cells cause a worse behavioral outcome than no Purkinje cell at all, explained by more important compensatory mechanisms at work with severer forms of atrophy. Since deep cerebellar nuclei are the only cell type sending information out of the cerebellum, paw-clasping may depend on the extent of damage to this area. As a result of Purkinje cell loss in *Grid2*^{Lc} mutants, there is anterograde degeneration of deep cerebellar nuclei by about 30% (Heckroth, 1994), presumably sufficient to initiate compensatory mechanisms in reticulospinal (Rose et al., 1993) and corticospinal (Whishaw et al., 1992) pathways, which, together with the cerebellum (Nowak et al., 2007), participate in object grasping. These mechanisms may include the basal ganglia.

4. Basal ganglia

Paw-clasping has been described in several murine models with anomalies in the basal ganglia, notably those affecting the *HDH* gene responsible for Huntington's disease. When lifted by the tail, R6/1 and R6/2 transgenic mice mutated for the human *HDH* gene with neuropathology in dorsal striatum, display hindlimb clasping (Mangiarini et al., 1996). The abnormal reflex appeared earlier in the R6/2 line than R6/1, presumably due to greater polyglutamatine expansion in the former, 150 CAG repeats versus 115 CAG repeats of the truncated human gene. Paw-clasping was also reported in transgenic mice mutated for the human *HDH* gene with 89 and 48 CAG repeats (Reddy et al., 1998). On the contrary, the anomaly was not detected in mice with only 16 CAG repeats. Likewise, knockin mice mutated for the murine *Hdh* gene with 150 CAG repeats exhibited paw-clasping and the bat-like posture (Heng et al., 2007; Lin et al., 2001), whereas such reflexes were absent in *Hdh*Q111 (Wheeler et al., 2002) or *Hdh*Q71 and *Hdh*Q94 (Menalled et al., 2000, 2002) mice with fewer polyglutamatine repeats. Thus, the extent of polyglutamatine expansion has a functional impact on clasping responses. Nevertheless, because the normal gene is highly expressed in extrastriatal regions such as the cerebellum and neocortex (Landwehrmeyer et al., 1995; Li et al., 1993), it remains to be determined whether these areas contribute to paw-clasping in murine models of Huntington's dementia.

In favor of a basal ganglia contribution is the finding that the same anomaly occurs in mice with striatal pathology caused by a mutation of a separate gene, namely *Dync1h1*^{Cra1} (Braunstein

et al., 2010) described above, though this mutant is also characterized by dorsal spinal pathology (Dupuis et al., 2009). Moreover, limb clasping in mice (Fernagut et al., 2004) and hamsters (Canonaco et al., 2005) was observed after striatal lesions caused by systemic administration of 3-nitropropionic acid, a neurotoxic agent also affecting the substantia nigra pars compacta (Fernagut et al., 2004). A contribution of dopamine to limb clasping is indicated by potentation of the effect of 3-nitropropionic acid after administration with MPTP (methyl-phenyl-tetrahydro-pyridine), destroying midbrain dopaminergic neurons (Fernagut et al., 2004). However, paw-clasping, to our knowledge, has not been described to date in any transgenic mouse model of Parkinson's disease, and so it is uncertain whether dopamine depletion alone can trigger it. Stereotyped grasping in humans (see below) is rather associated with neuroleptic-induced tardive dyskinesia, and therefore with faciliation of dopamine transmission (Kaneko et al., 1993), and so the MPTP potentiation in mice is probably due to acute facilitation of dopamine transmission as opposed to long-term inhibition.

5. Multiple levels: forebrain, midbrain, and hindbrain

Paw-clasping has been demonstrated in transgenic mice expressing *Prp* (prion protein) combined with its own pan-neuronal promoter, calcium-calmodulin-depending kinase (CAMKII), which reduces neocortical thickness (Wang et al., 2009). The pathological reflex also occurs in several models with null mutations. Brain-derived neurotrophic factor (BDNF) is normally expressed throughout the brain. Knocking out this gene is lethal, but when it is restricted to the telencephalon, causing reduced striatal volume, the mice are viable and display hindpaw clasping (Baquet et al., 2004; Strand et al., 2007), as do mice deficient in *Bdnf* in brainstem, the normal gene being normally expressed in susbtantia pars compacta, cerebellum, and dorsal root ganglia (Baquet et al., 2005). The same phenotype occurs in a conditional *Bdnf* knockout mediated by Cre recombinase inserted in the *Mapt* (microtubule associated protein tau) gene expressed in postmitotic neurons (Rauskolb et al., 2010).

Another conditional knockout exhibiting paw-clasping is the *Atg7* (autophagy-related 7) model crossed with transgenic mice expressing Cre recombinase under control of the *Nes* (nestin) promoter to produce deficiency specifically in the central nervous system, causing degeneration in neocortex and cerebellum (Komatsu et al., 2006). In addition, fore- and hindpaw clasping with ataxia was evoked in a conditional knockout for *Dicer1* in dopaminoceptive neurons by using a D1 dopamine receptor Cre recombinase (Cuellar et al., 2008). Likewise, paw-clasping occurs in other null mutants affecting multiple brain regions: *Foxb1* (forkhead box 1) with retarded growth in midbrain and diencephalon (Labosky et al., 1997), *Hexa*, encoding hexosaminidase A, normally expressed in multiple brain regions and when mutated responsible for Tay-Sachs disease (Miklyaeva et al., 2004), *Cav1* (caveolin-1) with a smaller brain but no obvious morphological anomaly (Trushina et al., 2006), and *Npr2* (natriuretic peptide receptor 2) possibly due to compression of the medulla by skull deformities (Tamura et al., 2004). Moreover, the same phenotype occurs in *Mecp2* conditional knockouts of a gene encoding methyl-CpG binding protein 2 (Santos et al., 2007), mutated in Rett syndrome (Dunn and MacLeod, 2001), the mice with abnormal synaptic activity in thalamus and motor cortex (Wood and Shepherd, 2010; Zhang et al., 2010). Likewise *Mef2c* conditional knockouts show paw-clasping (Li et al., 2008), encoding myocyte enhancer factor 2, a transcription factor proposed to act downstream of MECP2. The authors hypothesize a relation between paw-clasping and hand-wringing, a prominent motor phenotype in patients with Rett syndrome (Dunn and MacLeod, 2001).

6. Mouse models of Alzheimer's disease

Paw-clasping has been described in transgenic mice with amyloid pathology caused by mutations of *APP* (amyloid precursor protein), experimental models of Alzheimer's disease. APP_{751}SWE (APP23) transgenic mutants with the Swedish mutation displayed paw-clasping, whereas no control on the C57BL/6J background did so (Lalonde et al., 2005b). The same pathological reflex was seen in APP_{695}SWE mutants (Tg2576) (Lalonde et al., 2003). However, as mentioned above, wild-type C57B6/SJL littermates on the same genetic background as this mutant displayed the same sign, though fewer, presumably as a consequence of SJL genes. Hindlimb clasping was also reported in APP_{751}SL+*PS1*/M233+L235P knockin mice with Aβ plaques and axonal neuropathology in brain and spinal cord (Wirths et al., 2007), but not, despite the presence of Aβ plaques, in APP_{695}SWE/co+*PS1*/ΔE9 mutants, indicating that amyloid pathology does not necessarily lead to paw-clasping (Lalonde et al., 2004).

Because the same phenotype appears in *5htt* mutants lacking the 5-hydroxytryptamine (5HT, serotonin) transporter (Lira et al., 2003), elevated 5HT concentrations at the synapse may trigger paw-clasping. This may be one mechanism underlying paw-clasping in mice with Alzheimer-like pathology, since APP_{751}SWE mice have higher brain 5HT concentrations than wild-type (Van Dam et al., 2005).

7. Human neurological symptoms

As mentioned above, a parallel has been drawn between paw-clasping and hand-wringing displayed by patients with Rett syndrome (Li et al., 2008) with diffuse lesions in neocortex, basal ganglia, and cerebellum (Carter et al., 2008; Dunn and MacLeod, 2001), though the human phenotype lacks the postural component present in mice. Likewise, a parallel may be drawn between paw-clasping and involuntary grasping of objects, a frontal-lobe release sign occurring in infants (Schott and Rossor, 2003), even in utero (Jakobovits, 2009). In infants, palmar (Lantz et al., 1996) and plantar (Futagi and Suzuki, 2010) grasping probably occurs as a result of immature inhibitory connections between non-primary motoneurons in brain and spinal interneurons, leading to release of inhibition (Futagi and Suzuki, 2010). In adults, lesions of supplementary motor cortex or anterior cingulate but not primary somatosensory cortex cause palmar grasping (De Renzi and Barbieri, 1992; Hashimoto and Tanaka, 1998). It is

presumed that damage to supplementary motor cortex disconnects cingulate-mediated volition from the pyramidal projection. The effect is contralateral to the lesion, due to an ipisilateral projection from supplementary motor cortex to primary motor cortex followed by a contralateral projection to spinal cord, terminating in α-motoneurons responsible for hand movements.

As a result of neocortical damage, the grasp reflex is observed in patients with Alzheimer's disease (Souren et al., 1997), up to 7% of them in one series ($n=161$) (Burns et al., 1991), but perhaps even more prevalent in patients with Lewy body dementia (Borroni et al., 2006), possibly because of added damage to the basal ganglia. The pathological reflex is present in Parkinson's disease (Pearce et al., 1968), in 10% ($n=21$) of patients with stages 3 and 4 of the Hoehn and Yahr scale but not those in stages 1 and 2 ($n=27$) (Huber and Paulson, 1986) or those with an average Hoehn and Yahr scale of 2.3 ($n=25$) (Vreeling et al., 1993). The reflex is also present in patients with Huntington's chorea, evaluated as part of frontal assessment battery scores correlated with cognitive performance (Rodrigues et al., 2009 and personal communication). The presence of primitive reflexes serves as a predictor of cognitive performance in Parkinson's disease (Huber and Paulson, 1986) and Alzheimer's disease (Franssen et al., 1993), as well as patients suffering from traumatic brain injury (Wortzel et al., 2009). In particular, grasping scores were linearly correlated with a frontal lobe-mediated cognitive test in patients with schizophrenia (Hyde et al., 2007).

In contrast to the above-mentioned signs, a postural component is present in the pathological placing response, whereby the dangling foot of the patient is involuntarily placed on a horizontal surface (Botez, 1976). As in the normal placing response of rodents held by the tail, this pathological reflex can be elicited either by visual or tactile cues. Unlike the human grasping response, the human placing reflex occurs ipsilateral to the lesion, presumably because of neocortical regions afferent to the motor cortex projecting to the opposite hemisphere. Moreover, unlike the grasping reflex, the placing reflex involves the parietal lobe, in particular the postcentral gyrus.

8. Animal–human parallels

As with human grasping and placing reflexes and the hand-winging stereotypy, rodent paw-clasping may be due to a disconnection between premotor and motor cortex. This hypothesis can be tested by determining whether lesions of premotor cortex in mice elicit paw-clasping, not yet been attempted to our knowledge. From data on murine mutations, paw-clasping and the bat-like posture appear with lesions of cerebellum, basal ganglia, and neocortex. The underlying mechanism appears to comprise cerebello-cortico-reticular and cortico-striato-pallido-reticular pathways, possibly mediated by changes in monoaminergic transmission to these brain regions, in particular noradrenaline and 5HT. More accurate observations of this phenotype will help not only in distinguishing mutant from non-mutant animals but also in identifying where in the nervous system the gene is likely to function.

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