The human motor cortex microcircuit: insights for neurodegenerative disease

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TOC Summary

The human motor cortex is selectively vulnerable in a number of neurodegenerative diseases. In this review McColgan et al. integrate layer-specific physiology and pathobiology in the motor cortex thereby generating hypotheses that can be tested in humans using ultra-high resolution neuroimaging techniques.

Glossary

Anti-sense oligonucleotide therapies – These are single stranded DNA molecules, which bind to target pre-mRNA and recruit RNAse H causing degradation of the complex. This approach has already been applied to a number of neurodegenerative disease including Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis and Alzheimer's disease.

Fusiform – This refers to a spindle shape, which is wide in the middle and tapers at both ends.

Piriform – This refers to a pear shape, from the latin from *pirum* "pear" and *forma* "shape".

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) – This is a compound which can cross the blood brain barrier were it is then converted into 1-methyl-4-phenylpyridinium (MPP+), a neurotoxin, which causes selective and permanent destruction of dopaminergic neurons in the substania nigra.

Vibrotactile discrimination – This is an experimental design were stimuli of two different frequencies are applied to the hand and the participant is asked to discriminate between the low and high frequency stimuli.

Infragranular layers – These are cortical layers 5 and 6, which are below the granular layer 4 in the neocortex.

Supergranular layers - These are cortical layers 1 to 3, which are above the granular layer 4 in the neocortex.

Hyperkinetic – This relates to increased or excessive movement, such as tremor in Parkinson's disease or chorea in Huntington's disease

Hypokinetic – This relates to reduced or slowed movement, such as reduced fine finger movements and rigidity seen in Parkinson's disease.

Magnetic resonance spectroscopy – This technique detects radiofrequency electromagnetic signals that are produced by the atomic nuclei within molecules. It can be used to obtain measures of chemicals in the brain, such as N-acetylasparate, creatine, glutamate and GABA.

Abstract

Human motor cortex comprises a microcircuit of five interconnected layers with different cell types. Here we use a layer- and cell-specific approach to integrate physiological accounts of this motor cortex microcircuit with the pathophysiology of neurodegenerative diseases affecting motor functions. In doing so we can begin to link motor microcircuit pathology to specific disease stages and clinical phenotypes. Based on microcircuit physiology, we can make future predictions of axonal loss and microcircuit dysfunction. With recent advances in high-resolution neuroimaging we can then test these predictions in humans in-vivo, providing mechanistic insights into neurodegenerative disease.

Introduction

Motor cortex undergoes selective degeneration in neurodegenerative diseases including Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS). To date, relatively little is known about how these diseases affect specific layers and cells of the human motor cortex, and the corresponding inter- and intra-layer connectivity of the motor microcircuit. This is due in part to layer- and cell-specific accounts of motor cortex pathophysiology being limited to animal models and post-mortem studies. However, animal models develop disease typically over months to years, whereas human neurodegenerative disease proceeds over many decades[1,2]. Furthermore, post-mortem studies can only capture the end-stage of the disease process[3]. Providing a definitive account of selective motor cortex degeneration will require the study of neurodegeneration in-vivo in humans at the presymptomatic and early stages of the disease, when therapies can be delivered prior to irreversible neuronal loss.

Here we link physiological accounts of the motor cortex microcircuit with cell- and layer-specific changes in animal models and human post-mortem studies. We demonstrate how these can be used to make disease-specific predictions of axonal loss based on the normal physiology of the motor microcircuit. We then describe how we can test these predictions using recent advances in ultra-high resolution human neuroimaging methods. Finally we describe the utility of this approach in the context of neurodegenerative disease and emerging antisense oligonucleotide therapies, which are likely to have greatest impact in cortical regions including the motor cortex.

Organization of motor cortex layers

Cytoarchitectonics

Cytoarchitechtonics describe the cellular composition of cortical tissue from the pial surface to the grey–white matter boundary. The mammalian neocortex is conventionally divided into 6 layers based on cell type, cell size and cell density, although further subdivisions exist depending on various properties across the depth of the cortex (see figure 1). Layer 1 (L1), the molecular layer, contains few cells of fusiform or piriform shape as well as glial and vascular endothelial cell nuclei. L2, the external granular layer, contains densely packed pyramidal cells and smooth cells. L3 contains large pyramidal cells. L4, the internal granular layer consists of small densely packed pyramidal cells, with the exception of the primary visual and somatosensory cortices, which contain spiny stellate cells in humans. L5, the inner pyramidal cell layer contains pyramidal cells. L6, the fusiform layer consists of densely packed spindle shaped cells[4].

The human primary motor cortex controls voluntary movement via descending projections to the spinal cord and is located anterior to the central sulcus[5] The motor cortex was originally termed area 4 by Brodmann and is described as agranular, since it is characterised by an absence of visible granular L4 cells[6]. The motor cortex may be further sub-divided, where L1 is divided into L1A and L1B based on cell density. L3 is divided based on cell size, with small pyramidal cells in L3A, medium pyramidal cells in L3B and large pyramidal cells in L3C. The cytoarchitectonic space for L4 is defined as $L3_{(4)}$ and $L5_{(4)}$, Small pyramidal cells are found in $L5_{(4)}$, followed by the medium and large size pyramidal cells of layer L5A. Below these cells are found giant pyramidal cells or Betz cells in L5B, which are the largest cells in the cerebral cortex. Betz cells characterise the human motor cortex and are assumed to support long-range cortico-motoneuronal projections to the digits and anti-gravity muscles[7]. Layer 6 is sub-divided into L6A and L6B and contains fusiform cells[8].

The motor cortex in non-human primates and rodents follows a similar agranular layer structure to that in humans. Seminal studies in motor cortex layer organisation focus on the rodent motor cortex, where invasive cellular resolution imaging methods can be used to study cortical layers in exquisite detail. These findings largely generalise to other mammalian species. In mice, L2 and L3 are usually grouped together, due to their comparable pyramidal cell populations, and are referred to as L2/3. Below L2/3, layer 5 (L5) is subdivided into superficial layer 5A (L5A) which contains medium and large size pyramidal cells and deeper layer 5B (L5B)[9], which contain large cortico-spinal motor neurons homologous to Betz cells in primates and other higher mammals.

Myeloarchitectonics

Complementary to cortical layer cytoarchitectonics, myeloarchitectonics describes the distribution and trajectory of myelinated fibres in the cortex ~~(Fig. 1)~~. In the human primary motor cortex (M1) higher fibre density is seen in deeper layers as the number and size of pyramidal cells increase from myeloarchitectonic layers 3 to 5. Myeloarchitectonic layer 1 contains myelinated fibres that run horizontally, whereas myeloarchitectonic layers 4-6

contain dense myelinated fibres running vertically[10]. Parallel to this intra-cortical axonal organisation, the dendritic arborization of pyramidal cells is layer-specific. Although all cortical pyramidal neurons typically display an apical dendrite reaching up to the pial surface of the cortex, alongside basal dendrites branching from the soma, pyramidal neurons in L2 and L3 present with less extensive dendritic branching than their deeper counterparts[11]. Pyramidal neurons in motor cortex L5A and especially L5B have thick vertically oriented apical dendrites reaching through the upper layers up to the pia[7,12,13].

Motor cortex cell type

Although cytoarchitectonics initially focused on the granular, stellate and pyramidal cells, cells across the layers of the cortex can be classified into a number of different subtypes. The most basic classification distinguishes excitatory pyramidal cells and inhibitory interneurons. Glutamate is the main excitatory neurotransmitter whereas GABA is the main inhibitory neurotransmitter[14] in the mammalian nervous system.

Pyramidal neurons

In the rodent brain, pyramidal cells account for 80% of cortical neurons, and can be further sub-divided into Intra-telencephalic (IT) and Pyramidal tract (PT) neurons based on their projection targets[15]. IT neurons are located in L2-6 (L2/3, L5A, L5B, L6 in the rodent motor cortex) and project both ipsilaterally to the striatum and contralaterally to the striatum and cortex. IT neurons therefore include both cortico-striatal and cortico–cortical projections. These IT cortico-cortical projecting neurons represent a broad range of different neuronal types that project within the neocortex. For example some IT neurons make inter-hemispheric connections via the corpus callosum and anterior commissure, and are correspondingly called callosal/commissural projection neurons (CPN)[15,16]. A detailed discussion of these IT subtypes is beyond the scope of this review and we direct readers to[16] for further information.

PT neurons and Betz cells are found exclusively in L5B, in primates and form both cortico-striatal and cortico-spinal connections[17]. Betz cells are exclusive to M1, whereas PT neurons vary in size and are found throughout the cerebral cortex (Fig. 1a~~2a~~). Cortico-thalamic (CT) neurons are found in L6 and project exclusively to the thalamus[18]. These pyramidal cell subtypes can be further characterised based on electrophysiology[15] or transcriptomic signatures[19]. Although we acknowledge that a broad range of diverse neuronal sub-types exist within the IT–PT classification, this offers a framework for predicting cell-specific circuit alterations as disease selective effects on PT and IT neurons are commonly reported in the literature. Pyramidal cell loss, particularly in the motor cortex is seen in human neurodegenerative diseases and animal models including PD[20], HD[21] and ALS[22].

Interneurons

Interneurons form connections with PT and IT neurons and can be distinguished on the basis of the calcium-binding proteins they express. These include parvalalbumin (PV), somatostatin (SST), calbindin (CB) and calretinin (CR). PV and SST interneurons are the two main subtypes of interneurons inhibiting pyramidal neurons in motor cortex. PV and SST interneurons are found across all layers and act to inhibit pyramidal neurons in L2 to L6. PV interneurons tend to connect to the soma or perisomatic basal dendrites of pyramidal cells in the same layer, controlling action potential summation[23,24]. SST interneurons connect not only to the basal dendrites of pyramidal cells, but importantly also to the apical and tufting dendrites in upper L2/3 and L1 thanks to vertically-oriented axons ascending to the pia matter (Fig. 1b~~2b~~). Connectivity between interneurons and pyramidal neurons in M1 tends to be intra-layer, with interneurons connecting to pyramidal cells in the same layer as them[25]. Although there is some evidence that some SST interneurons located in lower layers can project across layers and reach L2/3[23], much greater inter-layer connectivity is seen in other cortical regions, such as the visual and somatosensory cortices[25]. SST interneurons in lower layers receive primarily inter-layer excitatory drive from L2/3 pyramidal neurons, whereas PV interneurons receive their excitatory input from neurons located in the same layer[26]. PV and SST interneurons thus form a dense network of connections[27] and are important in circuit integration and particularly in recurrent and feedback inhibition[23]. Given their contact with pyramidal distal dendrites, SST interneurons also prevent pyramidal cell over-activation[28]. Thus SST interneuron loss and dysfunction have been implicated in epilepsy[29], neurodegeneration[30] and psychiatric disorders[31] due to their role preventing neuronal hyperactivation.

Motor cortex layer connectivity

The canonical microcircuit

Gilbert and Wiesel[32] provided one of the first accounts of a simplified cortical microcircuit applicable across cortical areas. This was based solely on excitatory cells and proposed that thalamic input arrives at L4, excitatory cells in L4 project to superficial neurons (L2/3) and superficial pyramidal neurons (L2/3) project to L5, which projects to L6, with L6 neurons then projecting to L4[33] and the thalamus[34-37]. Douglas and Martin expanded on this foundation by introducing the concept of a “canonical microcircuit” which also included inhibitory cells, proposing this as a common circuit of cortical processing. The canonical microcircuit includes 3 distinct populations of neurons: excitatory superficial (L2/3) and deep pyramidal neurons (L5/6), and inhibitory interneurons[38].

The mammalian motor cortex is classically described as agranular with no visible L4, with a number of theories proposing that extrinsic input is not derived from the thalamus but from the neighbouring somatosensory areas in a top-down fashion[39]. However, this is undermined by demonstration of glutamate vesicle transporter VGluT2, a marker of thalamic terminal boutons, in L4 of rodent M1[40]. A recent study has highlighted the existence of connectivity patterns in the rodent motor cortex that are homologous to the canonical L4. Three criteria were chosen

for establishing layer 4 connectivity in the motor cortex (M1): thalamo-cortical input, output to L2 and L3 and a paucity of cortico–cortical long-range connectivity. The authors demonstrated in the rodent motor cortex that neurons at the L3/5a boundary in M1 fulfilled these criteria[41]. Furthermore, they showed that in contrast to stellate cells found in L4 of the S1, L3/5a in M1 contained only pyramidal cells. These findings have important implications for M1 microcircuit models as they involve the existence of a thalamo-cortical recipient population of pyramidal cells distinct from the superficial L3[42]. Whist it remains controversial, there is further evidence that L4 exists in the primate motor cortex[43,44]. This supports the concept or a canonical microcircuit generalisable across the cortex.

Layer and sub-layer connectivity

Layer connectivity in M1 is comprised of two inter-connected circuits, an upper closed loop circuit spanning L2-L5A and a lower closed loop circuit spanning L5B-L6. The upper loop receives thalamo-cortical excitatory input via L3 and neurons in L2 and L3 then project to L5A and L5B. L5 then projects excitatory output to the spinal cord and striatum[45] (Fig. 2ac).

With respect to sub-layer connectivity[17] IT neurons in L2 and L3 project to L5A IT neurons and L5B PT neurons in specific parallel pathways. L3 projects strongly to L5B PT neurons and marginally to L5A IT neurons. IT neurons in L2/3 project to IT neurons both ipsilaterally and contralaterally suggesting that IT neurons in L5A can receive input from both ipsilateral and contralateral sources, whereas PT neurons receive their input from ipsilateral L2/3. The findings from these connectivity studies can be combined to provide a schematic of the motor microcircuit (Fig. 2bd). This will form the basis for predictions of axonal loss and microcircuit dysfunction in neurodegenerative pathophysiology described in the next section.

Connectivity within the deep layers is also determined by cell type. There is an asymmetry in the connectivity between IT and PT neurons in L5, with IT neurons heavily projecting to other IT neurons in the same layer and to PT neurons, whereas PT neurons have lower recurrent excitatory connectivity amongst themselves and little to no projections to IT neurons[46]. This places IT neurons upstream of their PT counterparts in microcircuit connectivity, which will be a determining factor in terms of disease predictions.

Functional implications

The functional motor microcircuit cannot be envisioned separately from its connections to other cortical areas. Predictive coding theory[47] provides a functional role for feedforward and feedback connections respectively between areas. It posits that brain areas receive signals about external stimuli from feedforward connections to that area, but interpret these signals based on a priori predictions from previous experiences via feedback connections from higher brain areas[48-50]. In motor cortex, these computational accounts of function are only meaningful when considering M1 in relation with other areas involved at different levels of motor control, such as the sensorimotor and primary sensory S1 areas. Extrinsic inputs to M1 target selective layers and cell types in the microcircuit. Tracer experiments in rodents have shown that sensory to motor projections target L2/3 preferentially, and sensory thalamus targets L2/3 and L5A. The motor thalamus projects to L2/3 and L5 and acts as an intermediary for the striatum and cerebellum, which are involved in motor planning and motor action[51], respectively.

Motor learning

Normal motor function relies on the ability to adjust movement based on evolving sensory feedback; a function termed "motor learning". Based on the relative strengths of inter-layer connectivity pathways within the motor cortex detailed above, recent experiments suggest that upper L2/3 receive somatosensory projections and combine sensory feedback with existing motor representations[52]. As for the deeper layers, enhanced spine turnover of L5 neurons but not in L2/3 neurons occur during motor learning[53]. This suggests that Layer 5A pyramidal neurons encode evolving motor representations driven by sensorimotor integration at the level of L2/3. Specific localisation of this type of functional process is clinically relevant since impaired motor learning has been demonstrated in animal models of PD, where dopamine loss is associated with aberrant spine plasticity on the dendrites of L5 pyramidal neurons[54].

Bridging circuits and systems

Cerebral cortex neurophysiology

Animal models of neurodegeneration have significant limitations, particularly as these diseases are closely linked to normal aging. Neurodegeneration likely accumulates over several decades, while mouse models typically live only a few years. Similarly, PD non-human primate models created using MPTP involve an exogenous toxin, which has an immediate effect. It is therefore vital to study neurodegeneration in-vivo in humans. To do this we must understand how cortical microcircuits at the cellular level influence the function of whole brain networks at the systems level.

Ensembles of neurons produce electrical signals, which manifest as neurophysiological oscillations at a range of different frequencies. These are classified into five different frequency bands: delta (2-4 Hz) theta (5-7 Hz) alpha (8-12) beta (15-19 Hz) gamma (30-59 Hz). In animals these frequencies can be measured using single electrodes or multi-electrode arrays that measure local field potentials and multi-unit activity respectively. Importantly these frequencies can also be measured in-vivo in humans using electroencephalography (EEG) and magnetoencephalography (MEG). This provides an opportunity to link the anatomical layer- and cell-specificity of electrode recordings in animal models with human EEG/MEG measurements[55].

Post-synaptic potentials (PSPs) produce electrochemical currents. These can be measured as electrical potentials using EEG, however these signals are affected by differences in conduction across skull and scalp. PSPs also generate magnetic induction, which can be detected using ultra-sensitive MEG sensors. Although this signal has lower signal-to-noise ratio it is homogenous across brain, skull and air allowing for clearer interpretation of the anatomical location of brain signals[55]. A minimum of 10,000-50,000 cells are required to produce a detectable MEG signal[56]. Classically, specific frequency bands measured by EEG or MEG are associated with a range of specific physiological processes, such as a peak in the alpha frequency during eye closure, a peak in gamma during visual stimulation and a reduction in beta during movement followed by a rebound[55,57].

Seminal studies of neuronal oscillation frequencies in visual cortex suggest that oscillation frequencies are layer-specific and to some extent function-specific, with gamma frequencies localising to supragranular (L2 and L3) and granular layers (L4B) in V1[58-60]. Visual cortex studies provided the foundational evidence for the functional specificity of oscillation frequency bands, with the association between gamma and feedforward and beta and feedback cognitive processes[61]. There is some evidence that these findings may be generalizable to other cortical regions, such as the prefrontal cortex, during maintenance and control of working memory[62].

The beta range of frequencies is associated with motor control. Voluntary movement suppresses beta followed by a post movement beta rebound (PMBR)[63] .The transient increase in beta oscillations seen following voluntary movement, PMBR, has been localised to the motor cortex[64]. At the layer and cellular level, beta oscillations are seen in PT neurons in M1 during a grip task in non-human primates[65,66], thus further localising beta to L5B of M1.

Beta is generated in association cortices following excitatory stimulation by glutamate providing further evidence of the functional relationship between beta oscillations and pyramidal cells[67]. Beta synchronisation occurs across brain regions including the parietal, somatosensory and motor cortices[68], suggesting involvement of IT neurons as they form cortico-cortical connections. The function of these beta oscillations support higher motor cognitive processes such as vibrotactile discrimination[69]. Although alpha also localises to the infragranular cortical layers in the somatosensory cortex, this is thought to have an inhibitory influence in somatosensory processing suggesting a link with inhibitory interneurons[70].

The layer- and cell-specificity described above in animal electrophysiology studies translates to human studies. MEG and EEG experiments demonstrate that the generation of beta in the motor cortex is associated with motor-related decisions[71,72], which supports the role of beta in feedback activity demonstrated in non-human primates[61]. Furthermore alpha and gamma oscillations in the occipital lobe occur during visual tasks[73-78]. Indirectly this suggests similar layer-specificity for alpha, beta and gamma across animals and humans. This has also been tested more directly using anatomically specific MEG. This study revealed that alpha and beta localise to the grey-white matter boundary corresponding to infragranular layers, whereas gamma localises to the pial surface close to supragranular layers, both in the visual and motor cortices[79]. The association between gamma and interneurons has also been demonstrated in humans using magnetic resonance spectroscopy (MRS), where GABA concentration in M1 correlates with movement related gamma synchrony[80]. MEG can therefore provide proxy measures of infragranular and supragranular cortical layer physiology, which may be related to specific cell types.

Motor circuit pathology

Selective degeneration of specific neuronal types in the motor cortex leads to motor symptoms in PD, HD and ALS. Recent studies in rodents and non-human primate disease models have provided insight into how the motor cortex microcircuit is affected by cell-specific dysfunction and loss. When considered with human post-mortem data, a picture is emerging of how changes in the motor microcircuit results in human disease.

Parkinson's disease

Pathobiology

PD is a progressive neurodegenerative disease. At the cellular level it is characterised by loss of dopaminergic neurons in the substantia nigra pars compacta, leading to dopamine depletion in the direct and indirect pathways of the basal ganglia[81]. The clinical phenotype consists of asymmetric bradykinesia, rigidity and tremor. There are two main sub-types of PD, a tremor-dominant phenotype with the relative absence of other motor features, and a non-tremor dominant phenotype, characterised by a gait disorder and postural instability[82]. The tremor dominant phenotype is hyperkinetic whereas the non-tremor dominant is hypokinetic. Although replacement of dopamine alleviates the motor symptoms in PD, chronic dopamine therapy can lead to uncontrolled levodopa-induced dyskinesias (LID). This is a drug-induced disorder distinct from both tremor-dominant and non-tremor dominant PD phenotypes. Layer- and cell-specific changes have been studied in rodent hypokinetic PD models and the hyperkinetic LID model, revealing differences in electrophysiology[20,83] and morphology[84,85].

Electrophysiology of the basal ganglia in PD reveals abnormal excessive oscillatory synchrony in the beta band frequency generated by the electrical activity of neuronal ensembles. These pathological beta oscillations can be modulated by dopaminergic therapy and deep brain stimulation (DBS), which improves PD symptoms[86]. Beyond the basal ganglia, cortical abnormalities are seen in M1, dorsolateral prefrontal cortex[87,88], anterior cingulate cortex[89], corpus callosum[90] and posterior cortical regions[91]. Although fewer studies have focused on the motor cortex compared to the basal ganglia, abnormal beta oscillations are also seen in L5 of M1[92]. These arise through hyperpolarisation of pyramidal cells driven by synaptic inputs from GABAergic interneurons. Abnormal beta oscillations can be modulated using DBS, resulting in clinical improvement[93]. Administration of 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces parkinsonism and is commonly used as animal model in PD. In non-human primates MPTP parkinsonism in M1 causes reduced resting firing rates, increased irregular firing patterns and increased rhythmic firing in the beta frequency range for PT neurons in L5B, whereas IT neurons are relatively unaffected[20]. During movement, PT neuron dysfunction causes abnormal motor kinematic encoding and motor timing[83]. Accordingly the 6-hydroxydopamine (6-OHDA) hemi-parkinsonian mouse model shows reduced activity of PT neurons in M1[94].

Dendritic spine turnover in the motor cortex is directly related to motor learning in mice[53]. Dopaminergic innervation of L5 modulates these effects resulting in impaired motor learning in PD in mice models[54]. At the cortical level MPTP injection in mice impairs motor learning and increases calcium activity of dendritic spines in L5 PT neurons[95]. This is associated with reduction of SST interneuron activity, which inhibit L5 pyramidal neurons[23,96]. Stimulation of SST interneurons reduces the calcium dendritic spine activity of PT neuron dendrites and rescues motor learning[95]. Although these findings may seem contradictory to the reducing firing rates observed using electrophysiology in non-human primates[20], increased calcium activity may represent the increased irregular firing patterns not the reducing resting state activity observed, although direct comparisons have not been performed. Whereas the hypokinetic PD models show selective dysfunction of PT and SST interneurons in M1, with relative sparing of IT neurons, the hyperkinetic LID model shows involvement of both PT and IT neurons. 6-OHDA lesioned rats treated with chronic dopamine show enlargement of dendritic spines in IT[85] and PT[84] neurons. Based on these observations, we can begin to link layer- and cell-specific dysfunction in PD to clinical phenotypes (described below). Furthermore, based on microcircuit physiology ~~(Fig. 2d)~~ we can make predictions of how this dysfunction will affect other layers and cells in the cortex. One exception to this is tremor-dominant PD as there is a lack of animal models and human post-mortem cortex studies.

Circuit based predictions

The dying back[97-102] of axons and subsequent cell dysfunction and death of connecting neurons due to trophic factor deprivation[103,104] is well established in neurodegenerative disease (Fig. 3). Indeed many therapeutic strategies in neurodegeneration are aimed at the restoration of trophic factor loss[105,106]. Based on this observation we can predict how the loss of a cell population in one layer may affect other intra- or inter-layer cell populations. For example, the MPTP non-human primate model has a hypokinetic phenotype and shows selective dysfunction of PT neurons in L5B. PT neurons in L5B receive strong connections from IT neurons in L3 (Ref. 17) therefore dysfunction of PT neurons in L5B may lead to dysfunction of connections to ipsilateral descending connections especially L3, as well intra-layer IT to PT projections (Fig. 4~~(a)~~ and 4~~(b)~~). As the hyperkinetic LID phenotype involves PT and IT neurons we could therefore predict that PT dysfunction will lead to ipsilateral L3, and IT dysfunction will lead to contralateral L2 connection loss. Loss of the recurrent connections of IT neurons also leads to amplified intra-layer connectivity depletion (Fig. 4~~(c)~~ and 4~~(d)~~). With regards to projections outside the motor cortex, dysfunction or loss of L5B PT neurons are predicted to affect their upstream projections from the frontal areas[107].

Huntington's disease

Pathobiology

HD is a monogenic dominantly inherited neurodegenerative disorder, which initially leads to degeneration of the caudate and putamen in the basal ganglia. This results in cognitive, neuropsychiatric and movement deficits. HD is caused by a CAG repeat expansion in the huntingtin gene (*HTT*), which produces the pathogenic *HTT* protein. As HD is fully penetrant and monogenic it is possible to predict who will develop the disease with certainty. This allows study of how the disease affects the brain decades before symptom onset, which is not possible in the common sporadic neurodegenerative diseases such as (Alzheimer's disease) AD, PD and ALS. In HD, alterations in the caudate and putamen of the basal ganglia and visual and motor cortices occur over 10 years before the disease manifests[2,108]. In contrast to PD, the indirect basal ganglia pathway is selectively vulnerable in HD, resulting in increased activation of thalamo-cortical connections. This manifests clinically as uncontrolled choreiform movements. Involvement of the direct pathway occurs later in the disease and results in hypokinetic movement[109]

Pathological cortical changes in HD show close correlations with symptomatology. Post mortem studies, typically at the end stage of the disease, show prominent loss of pyramidal cells in layers L3, L5 and L6 in the primary motor[21,110], superior frontal[111,112], dorsolateral prefrontal[113-115], anterior cingulate[21,111], angular gyrus[116] and visual cortices[113,117,118]. Similar findings are seen in HD animal models[119]. Post-mortem studies typically use the SMI32 antibody, which stains pyramidal cells with long range connections, and therefore cannot differentiate PT from IT neurons[120]. More recently loss of corpus callosal axons has been demonstrated in the YFP(J16)-R6/2 HD mouse model, where the cell bodies of these axons co-localise SATB2, a marker of IT neurons[102]. This converges with evidence from large HD neuroimaging studies, including TRACK-HD[2,121-124] and PREDICT-HD[125,126], that both cortico-striatal and corpus callosum white matter is affected many years before disease onset in HD. Given that cortical IT neurons project to the striatum and across the corpus callosum, we hypothesise that these are the most vulnerable pyramidal cell type in HD.

As with PD, interneurons are also affected in HD, as evidenced by human post-mortem studies[127,128] and animal models[129]. Distinct patterns of interneuron loss are seen in different cortical regions and are associated with specific clinical phenotypes. For example, patients with a motor predominant phenotype show selective loss of calbindin (CB) staining as well as pyramidal cells in both the motor (M1)[127] and sensory (S1)[128] cortices. In contrast those with a psychiatric phenotype show loss of CB, calretinin (CR) and parvalbumin (PV) staining interneurons in the anterior cingulate[127]. SST interneurons also express calbindin[130], suggesting similar populations of M1 interneurons are affected in PD and HD.

Circuit based predictions

We can also make cell and layer specific predictions in HD based on motor circuit physiology. For example, loss of IT neurons in L5A early in the premanifest stage of the disease will lead subsequent loss of ipsilateral and contralateral

connections from L2/3. As the disease progresses dysfunction of SST interneurons may lead to hyperexcitability of PT neurons resulting in changes in ipsilateral L3 connections. As with PD, loss of IT neurons leads to amplified intra-layer connectivity depletion in L5 (Fig. 5~~(a)~~ and 5~~(b)~~). In terms of inter-areal connectivity alterations, loss of IT neurons specifically may result in the early loss of sensorimotor projections to the motor cortex.

Amyotrophic lateral sclerosis

Pathobiology

ALS is a progressive neurodegenerative disorder in which upper and lower motor neurons degenerate leading to paralysis of voluntary muscles and ultimately death[131]. More than 95% of ALS cases show aggregation and nuclear depletion of transactive response DNA binding protein (TDP-43)[132-134]. Mouse models with TDP-43 loss or impaired function reproduce the pathological, electrophysiological and clinical characteristics of ALS[22,132,135-138]. The giant pyramidal cells of Betz in L5B of the primary motor cortex and the α-motor neurons of the lower brain stem and spinal cord develop TDP-43 pathology at the beginning of the disease process[139], along with pyramidal cells in L5 and L6 causing motor loss[140,141]. Additionally degeneration of the Betz cell apical dendrites[142] may result in loss of input from the striatum via the rostro-medial motor thalamus causing deficits in motor planning[51]. As in PD and HD, other cortical regions are also affected, including the anterior cingulate and dorsolateral prefrontal cortex[143]. Corpus callosum loss is also seen in post mortem and neuroimaging studies[144-148]. Although loss of L5B Betz cells is the earliest feature in the motor cortex, abnormalities are also seen in L3 and 5 pyramidal cells[149-152] and interneurons[143]. In keeping with the preferential loss of Betz cells in ALS, cortico-spinal white matter loss is seen in numerous neuroimaging studies. This suggests IT neurons are spared at least in the early stages of the disease with pyramidal cell layer 3 loss seen in more advanced stages at post mortem[148].

Circuit based predictions

Based on these observations we can make circuit-based predictions about intra- and inter-layer disease effects. Early selective loss of Betz cells causes degeneration of the cortico-spinal tract. Within the cortex we predict the loss of intra-layer IT connections to Betz cells in L5B. With regards inter-layer connectivity we predict that the vulnerability of Betz cell apical dendrites[142] causes degeneration of IT L2/3 neurons, which in turn causes degeneration of contralateral IT L2/3 connections, consistent with subsequent atrophy of the corpus callosum, which only contains IT axons (Fig. 5~~(c)~~ and 5~~(d)~~). Given the finding from rodent tracer studies that L5B PT neurons are specifically targeted by frontal cortical areas [107], it is to be expected that these direct frontal connections would be at risk of early degeneration along with the L5B PT neurons they project to. These predictions are limited by the following considerations: It is unclear whether the same frontal to M1 layer specific projections are at work in the human motor cortex, and if they are, it should be clarified whether those target L5B PT neurons are Betz cells. As Betz cells are

selectively vulnerable in ALS, this type of cell-type clarification is necessary, as it would determine the disease prediction.

Human motor cortex imaging

Human neuroimaging modalities such as MEG and ultra-high field (UHF) MRI and MRS can be used to test the circuit-based predictions of neurodegeneration outlined above. UHF MRI enables us to image the brain at sub-millimetre resolution in living humans. Combining this with quantitative MRI (qMRI) approaches, such as multi-parametric mapping[153], provides sensitive structural measures of myelin and iron across the layers of the cerebral cortex[154,155] at resolutions of 500μm[156]. For example effective transverse relaxation rate (R2*) is sensitive to both myelin and iron[153,155] and is measured units per second. In addition to brain structure UHF MRI can also be used to investigate layer-specific brain function. Standard functional MRI (fMRI) approaches using the blood oxygen level dependent (BOLD) signal have proved challenging given the contamination of the signal from large draining veins at the cortical surface[157]. However vascular space occupancy (VASO) contrast, an estimate of total cerebral blood volume (CBV) change[158], has demonstrated layer-specific fMRI in a number of cortical regions including the motor[159], somatosensory[160] and prefrontal cortices[161] at resolutions between 0.7-0.9mm^3. MRS has also benefited from advances in UHF MRI. This technique generates magnetic resonance (MR) spectra based on the nuclei of atoms in a given tissue. In doing this enables measurement of a range of metabolites including glutamate and GABA, which can be directly related to pyramidal and interneurons discussed in the previous sections. Metabolites are represented as peaks on the MR spectra in parts per million relative to a given reference molecule. Higher field strengths in this context enable better spectral resolution, increased signal-to-noise ratio and thus improved accuracy of metabolite detection[162,163].

MEG studies in both PD[164] and ALS[165,166] reveal changes in the beta frequency bands in the motor cortex, consistent with pathological changes in L5B and PT neurons seen in animal models[83]. In early PD greater beta power is seen in M1 during rest compared to controls[167] with greater suppression of beta seen in controls during isometric contraction of the contralateral forearm. Conversely lower M1 beta power is seen in the later disease stages[168,169]. In ALS, accentuated beta desynchronisation occurs during movement preparation followed by a delay in PMBR following movement[165]. To date MEG has not been used in HD. Beyond motor-related neurodegeneration, layer-specific models have been applied to MEG data in fronto-temporal dementia demonstrating superficial (L2/3) and deep (L5/6) layer dysfunction and sparing of L4 in the temporal[170] and frontal lobes[171]. This modelling approach allows direct inferences to be made about layer specific function.

In addition to MEG, cortical layer function can now be investigated using UHF MRI. This was first demonstrated in the motor cortex using cerebral blood volume functional MRI (CBV-fMRI). Participants performed four different tasks to activate different connections; tapping with touch (S1-M1, M1-cortico-spinal tract (CST)), tapping

without touch (M1-CST), touch only (S1-M1) and left hand tapping (contralateral M1-M1). This allowed resolution of cortico-cortical input from the somatosensory cortex and cortico-spinal output. Consistent with known anatomy, cortico-cortical input showed high fMRI signal in the superficial layers, whereas cortico-spinal output showed high fMRI signal in the deep layers[159] (Fig. 6). Thus, superficial layer activation observed with CBV-fMRI may be related to the high recurrent connectivity between IT neurons in L2/3, while the deep layer activation may be related to L5B and Betz cells forming cortico-spinal connections.

Motor cortex dynamics crucially depend on cell-type-specific interaction. In humans, the chemical signature of specific neuronal cells might provide a key to bridging cortical ensemble dynamics and isolated circuit components. UHF MRI has also led to developments in magnetic resonance spectroscopy (MRS). At 7T it is possible to detect glutamate, glutamine and GABA concentrations in-vivo[172]. This provides indirect measures of neuronal excitation and inhibition[173], which can be linked to pyramidal and interneuron cells respectively. This technique has been applied to a number of brain diseases, most commonly schizophrenia, where changes in glutamate and GABA are seen in the anterior cingulate[174-178] and may reflect losses in the cell populations, which contain these neurotransmitters. Fewer studies have been performed in neurodegenerative disease. In PD, higher levels of GABA is seen in the pons and putamen[179]. In manifest HD lower levels of N-acetylasparate (NAA), creatinine and glutamate are seen in the striatum[180,181]. To date cortical changes in PD and HD have not be assessed using 7T MRS. In ALS reduced glutamate concentrations are seen in the motor cortex[182] which is consistent with the loss of excitatory pyramidal Betz cells in layer 5B seen at post-mortem. In addition to 7T MRS, 7T MRI can provide measures of cortical layer structure. We have recently demonstrated high correlation between post mortem cortical layer cell count / cell staining and quantitative MRI (qMRI) R2*, a measure of myelin and iron, across the whole brain at 500μm resolution. R2* is also highly correlated with the regional expression of layer specific genes suggesting that it's a sensitive measure of cortical layer structure[156].

Application to therapies

Using a multimodal approach, UHF quantitative MRI measuring cortical layer structure can be combined with UHF fMRI and MEG to measure cortical layer function, and UHF MRS to measure pyramidal and interneuron activity of the motor cortex. This layer and cell-specific information can then be applied to the motor microcircuit in order to understand cortical processing in both health and disease (Fig. 7). In the context of neurodegeneration there is an urgent unmet need to understand disease effects on cortical processing and the potential for therapeutic cortical remodelling. This is related to the advent of antisense oligonucleotide therapies (ASOs).

ASOs can target and block the production of protein from specific genes by binding to messenger RNA (mRNA) and preventing translation to lower the level of a specific target protein. This type of therapy has been referred to as 'gene silencing', although this is a misnomer as they cannot turn off protein production completely. This

approach has already been applied to targeting Huntingtin (*HTT*)[183] mRNA in HD, super oxide dismutase (SOD1)[184] mRNA in familial ALS, the LRRK2[185] mutation in PD and microtubule-associated protein tau (MAPT) in Alzheimer's disease (AD)[186]. The first phase 1/2 randomised controlled clinical trial of an ASO in HD shows dose-dependent lowering of mutant *HTT* in cerebrospinal fluid (CSF)[187]; a phase 3 trial is in progress.

As ASO therapies are delivered intra-thecally into the CSF their uptake is greatest in the cortex, with lower uptake in deeper brain structures such as the basal ganglia[183]. To determine their efficacy we must therefore have precise anatomical measures of cortical layer structure and function. This is particularly important in symptomatic trials in neurodegeneration where we know the disease process has been ongoing for decades[188] as the cortical abnormalities are visible long before symptom onset. Therefore, therapeutic effects may be subtle in symptomatic patients. Conventional brain imaging predominantly relies on whole brain or region of interest analyses to detect disease effects. Combining measures of cortical layer structure (qMRI), layer function (MEG) and chemical signatures of specific cell types (MRS) is likely to be much more sensitive to the changes induced by disease and therapeutic effects. The motor cortex is a good candidate region in which to establish this approach, as it is the thickest cortical region thus enabling greater resolution of this structure than any other cortical region.

Conclusion and further directions

We have reviewed the layer and cell-specific structure and function of the motor cortex in both health and disease, focusing on the motor microcircuit. This enables us to make predictions about disease-related changes in PD, HD and ALS. We have outlined how these predictions can be tested in-vivo in humans using recent advances in UHF qMRI, MRS, fMRI and MEG. Finally, we highlight the importance of these approaches for generating anatomical precise cortical biomarkers for ASO protein lowering therapies, which are currently being trialled across a range of neurodegenerative diseases including PD, HD, ALS and AD.

We acknowledge that there are still many challenges in bridging the gap between the macro-scale and micro-scale in the study of neurodegenerative disease. However with evolving technology, and MRI systems with ever higher field strengths, we are getting increasingly close to in-vivo histology. This will enable us to link the cellular level with the systems level, thus providing mechanistic insights into neurodegeneration and generating anatomically precise biomarkers that can be used to assess therapeutic response even decades into the disease process.

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Figures and Legends

Figure 1. Generalised scheme of cortical layering in cyto- and myeloarchitecture (human). Roman numbers correspond to cytoarchitectonic layers, based on cell type distribution. Arabic numbers correspond to myeloarchitectonic layers, based on the distribution of myelinated fibres across the depth of the cortex. These myelinated fibres are the axons of the cells contained in the cortical layers. The distributions of cytoarchitectonic and myeloarchitectonic layers therefore overlap, although with differences in the nomenclature of subdivisions within layers. Cytoarchitectonic layers III to Vb present a concentration of myelinated fibers running vertically across them. (reproduced with permissions from Palomero-Gallagher et al[10].)

Figure 12. Motor cortex cell type and connectivity between layers of the motor cortex (rodent): (a). IT and PT-specific patterns of long-range connectivity: Pyramidal neurons can be classified on the basis of their projection targets: Pyramidal tract (PT) neurons (green) send their axons to the Cortico-spinal tract (CST). PT neurons also project collateral axons to the ipsilateral striatum including the Caudate (Cau), Putamen (Pu) and Globus Pallidus (GP). Intra-telencephalic (IT) neurons shown in pink exclusively project within the telencephalon. IT neurons send axons to both the ipsilateral (not shown) and contralateral striatum and cortex. Cau, caudate; P, putamen, GP, globus pallidus; CST, cortico-spinal tract. **(b). Inter-layer Inhibitory connectivity**: Interneuron types in the cortex can be distinguished by the calcium-binding protein they express: Somatostatin (SST) or Parvalbumin (PV). Both PV and SST interneurons are found in the deeper layers of the cortex. IT pyramidal neurons are found in L2, L3, L5A and L5B. PT neurons are found in L5B. Somatostatin SST interneurons receive inter-layer input from pyramidal neurons located in the upper layers and send intra-layer output to deep layer neurons as well as inter-layer output to upper layer pyramidal neuron dendrites and intra-layer input. PV interneurons (gold) in lower layers and upper layers (latter not displayed) receive and send intra-layer input and output. SST – Somatostatin, PV – Parvalbumin.

Figure 2. (c). Layer and cell specific schematic of M1 microcircuit: (a). Intra-hemispheric (IT) neurons are found in all cortical layers from L2 to L5B. Pyramidal tract (PT) neurons are only found in L5B. Connections are represented here as a simplified chronological series of events for clarity, from thalamic input to cortico-spinal output. *(1)i.* Cortico-thalmamlic projections are sent to the superficial layers L2/3. *(2)ii.* Reciprocal projections between L2 and L3 IT neurons form an upper loop. *(3)iii.* Descending projections from L2/3 to L5 IT and PT neurons. *(4)iv.* Lower loop: Reciprocal connections between IT neurons in L5A and L5B and unidirectional projections from IT to PT neurons. *(5)v.* Output stage: IT and PT output to the striatum and PT output to the cortico-spinal tract (CST). Orange – thalamus, green – pyramidal tract (PT) neurons, cyan – intra-telencephalic (IT) neurons, gold – striatum, grey – cortico-spinal tract (CST). Roman numerals - cytoarchitectonic layers, Numbers – sequence of information flow. **(bd). Cell-specific schematic of inter-layer connectivity in M1:** Starting in L2 we show reciprocal connections between IT neurons in L2 and L3, L2 IT neurons projects to IT neurons in L5A and to PT neurons in L5B. L3 IT neurons strongly project to PT neurons in L5B and to a lesser extent to IT neurons in L5A in deeper layers. IT neurons in L5A also project back up to L2/3 pyramidal neurons. Somatostatin (SST) and parvalbumin (PV) interneurons inhibit mainly L5 pyramidal neurons. CST,cortico-spinal tract. The weight of connections is represent by thickness of axons.

Figure 3. Schematic showing effect of post-synaptic neuronal death on presynaptic axons and neurons (human). Postsynaptic neurons provide trophic factors to presynaptic neurons. Trophic factors allow the survival and growth of the target presynaptic neuron. When the postsynaptic neuron dies, this causes trophic factor deprivation, which can provoke the death of upstream presynaptic neuron ~~(Black cross – physiological loss)~~. Within a densely interconnected cortical microcircuit, this principle predicts the direction and order in which different connections are affected following the death of a specific neuronal component in the circuit.~~.~~

Figure 4. **Layer and cell-specific connectivity loss in human Parkinson's disease (PD) and levodopa-induced dyskinesia (LID). (a)** PD: **initial stage.** Selective loss of pyramidal tract (PT) neurons in L5B, along with loss of SST interneurons (IN) in L5. **(b).** PD: **Predicted connectivity loss**. Following the principle that loss of one neuron leads to the degeneration of the axons which synapse onto it we can predict that death of PT neurons in L5B will induce loss of ipsilateral descending connections from L2/3 IT neurons and loss of intra-layer IT to PT connections in L5A and L5B (dashed ~~red~~ lines show axonal degeneration). **Layer and cell-specific connectivity loss in. (c) LID: Initial stage.** Abnormalities of both IT and PT neurons in L5. **(d). LID: Predicted connectivity loss.** Descending projections from L2/3 to L5 IT and PT are lost and IT to IT, and IT to PT connections within L5 are lost. Long-range inter-hemispheric projections from contralateral cortex to L5A IT neurons are also predicted to degenerate. Cortico-spinal tract (CST). Weight of connections represents thickness of axons, ~~dashed red lines show axonal degeneration.~~.

Figure 5. Layer and cell-specific connectivity loss in human Huntington's disease (HD) and human amyotrophic lateral sclerosis (ALS). (a). HD: Initial stage. Selective loss of ~~i~~Intra-telencephalic (IT)~~T~~ neurons in L3 and L5, and loss of SST interneurons (IN) across layers. **(b) HD: predicted connectivity loss.** IT neuron loss in L5 is predicted to lead to loss of intra-layer IT-to-IT connectivity. Loss of IT neurons in both L5 and L3 is predicted to cause loss of inter-hemispheric contralateral L2/3 projections to L3 and L5 (dashed ~~red~~ lines show axonal degeneration).~~.~~ **(c) ALS: Initial stage.** Betz cells in L5B degenerate in parallel with interneurons in the early stages of the disease with selective vulnerability of the apical dendrites of Betz cells. **(d) ALS: predicted connectivity loss.** Degeneration of Betz cells causes loss of L5B IT neurons. Betz cell somas are located in L5B and their apical dendrites reach up to the cortical surface. Loss of Betz cells are therefore likely to affect the entire depth of the cortical circuit. The strong descending connections from L3 to L5B are predicted to be affected, as well as the intra-layer connections onto Betz cell apical dendrites within L2/3. Following this predicted loss of L2/3 IT neurons, inter-hemispheric projections from contralateral L2/3 IT neurons are also lost. Cortico-spinal tract (CST). Weight of connections represents thickness of axons~~.~~. ~~dashed red lines show axonal degeneration.~~

Figure 6. Average layer-dependent fMRI responses in the motor cortex of all participants in response to four different sensorimotor tasks (human). (a) This is an example of how high-resolution fMRI can be used to test the layer-specificity of motor function, when combined with appropriate experimental design. The results illustrate changes in cerebral blood volume (CBV) activity and percentage blood oxygen level dependence (BOLD), two different functional MRI imaging techniques. The first condition, tapping with touch, involved pinching together the finger and thumb of the hand contralateral to the area of M1 investigated. This involves sensation resulting in 'input' to upper layers (L2/3) from S1 and premotor cortices, along with movement causing 'output' from the deep layers (L5B) to the cortico-spinal tract. Layer-specific activation shows two peaks of activity in L2/3 and L5B, particularly using CBV as compared to BOLD. The second condition, tapping without touch, involves the same pinching motion but without the fingers actually touching, causing reduced sensory 'input' compared to the previous task, with the same 'output'. Therefore there is reduced activation in the upper layers (L2/3). The third condition is touch only, where the fingers remain motionless, but are rubbed with a textured cushion causing medium 'input' with no 'output'. This passive sensation condition elicits activation of the superficial layers only. The fourth condition ipsilateral tapping, involves the same movement as in the "tapping with touch" condition but this time performed by the ipsilateral hand. This was associated with negative sensorimotor change in the superficial layer indicating trans-callosal inhibition, with a flat profile in the deeper layers. (b) Shows the corresponding graphs with change in CBV and BOLD on the y-axis and across cortical depth on the x-axis, going from the cerebrospinal fluid (CSF) at the top of the cortex to the white matter (WM) boundary at the bottom. Each line is the averaged value across participants with the shaded areas indicating standard error. Overall this experiment provides an in-vivo account of layer-specific input-output activity in M1 during movement, which is compatible with rodent and non-human primate studies (reproduced with permission from[159]).

Figure 7. In-vivo layer and cell-specific high-resolution neuroimaging in humans. Using a multimodal approach, ultra-high field (UHF) quantitative MRI measuring cortical layer structure can be combined with UHF functional MRI (fMRI) and magnetoencephalography (MEG) to measure cortical layer function, and UHF magnetic resonance spectroscopy (MRS) to measure pyramidal and interneuron activity of the motor cortex. This layer and cell-specific information can then be applied to the motor microcircuit in order to understand cortical processing in both health and disease. ***Top centre~~middle~~*** - MEG figure showing an example illustration of between-group differences in MEG total power. This shows a topographical plot of significant differences in total power in patients with epilepsy expressed as a percentage of the power of the healthy control group, where black dots indicate statistical significance and colours indicate percentage difference in power. Red indicates highest percentage difference, while green indicates the lowest. This has been reproduced with permissions from[189]. Red~~Blue~~ pyramids represent ~~cortical pyramidal~~intra-telencephalic (IT) neurons, connecting to pyramidal tract (PT) neurons, and sinusoidal lines represent neuronal oscillations measured by MEG. ***~~Bottom~~ Left*** - figure showing protein MRS in the human brain with peaks of the metabolites acetyl asparate (Naa), creatine (Cr) and choline (Cho) reproduced with permissions from[190]. This approach can be used to measure glutamate and GABA, the neurotransmitters of pyramidal neurons and interneurons (IN) respectively. ***~~R~~Bottom right*** - UHF fMRI figure showing layer-specific functional activation during a finger pinch task. This task involves sensation resulting in 'input' to upper layers (L2/3) from S1 and premotor cortices, along with movement causing 'output' from the deep layers (L5B) to the cortico-spinal tract. The colour represents change in cerebral blood volume (CBV), where yellow represents greatest change and therefore activation in both upper and lower layers. Reproduced with permissions from[159]. ~~Purple – IT neurons, Green – PT neurons, Red – interneurons.~~

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