— Abstracts —

Origin and evolution of the cerebellum

Yasunori Murakami

Graduate School of Science and Engineering, Ehime University, Japan

The cerebellum has been identified in all extant vertebrates. In particular, gnathostomes (jawed vertebrates) that inhabit aquatic or aerial environments possess well developed cerebellum. By contrast, in cyclostomes including lampreys and hagfishes, the cerebellum is less prominent, suggesting that a gnathostome-type cerebellum might have evolved in early vertebrates after a split from the cyclostome lineage. In mammals, the cerebellum emerges from the dorsal side of the hindbrain, and the cerebellar primordium is marked by some transcription factors such as *Ptf1a* or *Atoh1*. Expression of those genes and cellular organization in the cerebellar primordium have been observed in many gnathostomes. Thus, the developmental plan to produce a cerebellar cytoarchitecture could date back at least to the common ancestor of gnathostomes. However, presumptive cognates of *Atoh1* and *Ptf1a* could be identified in the lamprey and their expression domains are located in the dorsal side of the hindbrain as well as in gnathostomes. Thus, certain genetic background underlying the formation of the cerebellum might have been already established in the latest common ancestor of vertebrates. Then, the cerebellum is thought to diversified in gnathostome lineage in relation to the development of vestibular apparatus and the modification of body structures such as paired appendages.

The cerebellum of ray-finned fishes: specific features and diversity

Naoyuki Yamamoto
Hanako Hagio

Laboratory of Fish Biology, Graduate School of Bioagricultural Sciences, Nagoya University, Japan

The cerebellum of ray-finned fishes includes the valvula cerebelli that can be found only in this vertebrate group. The valvula protrudes rostrally into the mesencephalic ventricle. The size of the valvula cerebelli shows dramatic species differences, and the valvula of the elephantnose fish is gigantic to cover almost all of the other parts of brain. This hypertrophy may be related to the electric sense of this fish. Another specific feature is that cerebellar nuclei are lacking in teleosts, the largest taxon within ray-finned fishes. Instead, teleosts possess eurydendroid cells within or close to the Purkinje cell layer, which receive inputs from Purkinje and granule cells and project outside the cerebellum.

Ray-finned fishes possess cerebellar-like structures in the mesencephalon and medulla oblongata. The former is called the torus longitudinalis and associated structures in the optic tectum, and the latter the eminentia granularis and associated structures in the medulla oblongata. Both systems contain granular cells and Purkinje-like cells, the former giving rise to fibers similar to parallel fibers that synapse upon the dendrites of Purkinje-like cells. It is an interesting future study to search for the reasons why such cerebellum-like circuitries evolved to perform information processing that occurs in these structures.

Mechanisms underlying climbing fiber synapse elimination during postnatal cerebellar development

Masanobu Kano

Department of Neurophysiology, Graduate School of Medicine, The University of Tokyo / International Research Center for Neurointelligence (WPI-IRCN), The University of Tokyo Institutes for Advanced Study (UTIAS), The University of Tokyo, Japan

In the neonatal rodent cerebellum, Purkinje cells (PCs) receive excitatory synaptic inputs from multiple climbing fibers (CFs). PCs are initially innervated by more than five CFs with similar synaptic strengths. During the first three postnatal weeks, redundant CFs are eliminated and most PCs become innervated by single CFs. This developmental process, termed CF synapse elimination, consists of at least four distinct phases: (1) selective strengthening of a single CF out of multiple CFs innervating each PC from postnatal day 3 (P3) to around P7 (functional differentiation), (2) translocation and expansion of innervation territory of the strongest CF ('winner' CF) to PC dendrites from P9 (dendritic translocation), (3) elimination of somatic synapses of the 'winner' CF and those of weaker CFs ('loser' CFs) from P7 to around P11 (early phase of CF elimination), (4) elimination of remaining somatic CF synapses from around P12 to P17 in a manner dependent on excitatory synapse formation from parallel fibers onto PC dendrites (late phase of CF elimination). In this talk, I will make an overview about cellular/molecular mechanisms of CF synapse elimination, and present our unpublished data to discuss how neural activity regulates the distinct phases of CF synapse elimination.

Cerebellar Purkinje cell zones. Where and why.

Jan Voogd

Department of Neuroscience, Erasmus, mc Rotterdam, The Netherlands

There were three important considerations in the discovery of Purkinje cell zones in the cerebellum of cats and ferrets, reported in my thesis of 1964. First, compartments in the white matter were found to channel the Purkinjecell axons from a zone to a cerebellar or vestibular nucleus. These compartmnts could be delineated in Häggqvist-stained material, where small myelinated fibers accumulate at their borders, contrasting with the medium-sized Purkinje cell axons, or with acetylcholinesterase histochemistry, where the borders of th compartments stain more intensely. An Important consideration in the topography of the zones is Bolk's (1906) proposal of the mammalian cerebellum as consisting of the curved folial chains of vermis and hemiphere. Ogawa's (1935) division of the interposed cerebellar nucleus in anterior and posterior divisions was another important clue for the definition of the zones. Oscarsson stimulated the dissected funiculi and recorded climbing fiber evoked potentials from the anterior lobe, where they were located in several parallel longitudinal zones. The zones, defined by his spino-olivocerebellar climbing fibers paths, were found to be identical with the A, B, C1-3, D1 and D2 zones of my description. A zonal distribution of the epitope of the zebrin antibody (aldolase C, Hawkes and Herrup, 1995) was found to be partially congruent with these Purkinje cell zones (Voogd et al., 2003; Sugihara and Shinoda, 2004). Purkinje cell zones, therefore, are defined by their cerebellar or vestibular target nucleus, their innervation by climbing fibers from a particular subdivision of the inferior olive, their zebrin signature and their topography. Some aspects of the comparative anatomy of the zones, and of their functional topography, more in particular of the zones of the flocculus (van der Steen et al., 1994), will be discussed.

Structural magnetic resonance imaging (MRI) of the cerebellar nuclei in hereditary ataxias

Dagmar Timmann

Department of Neurology, Essen University Hospital, University of Duisburg-Essen, Germany

Our group has a long-standing interest in studying the human cerebellar nuclei in health and cerebellar disease. Susceptibility-weighted imaging (SWI) and Quantitative Susceptibility Mapping (QSM) are used to perform structural MRI of the cerebellar nuclei at conventional (3T) and ultra-high (7T) magnetic field strength. SWI and QSM data of the dentate nuclei is presented in different forms of hereditary ataxias. Focus is on spinocerebellar ataxias type 3 and 6 (SCA3, SCA6).

Funded by DFG TI 239/17-1; DE 2516/1-1

The lobular and striped organization of the cerebellar hemisphere in relation to projection patterns of afferent and efferent axons in rodents, with a special focus on crus I

Izumi Sugihara

Mohammad Shahangir Biswas, Gideon Anokye Sarpong, Yuanjun Luo

Department of Systems Neurophysiology, Tokyo Medical and Dental University, Japan

The cerebellum is compartmentalized into multiple transversely-arranged lobules and longitudinally-arranged stripes defined by molecular expression. How these structures are related to topographic axonal projection patterns and hence, to the functional compartmentalization of the cerebellum has not been fully clarified. Among the four lobules that occupy the most of the hemispheric area in the rodent cerebellum (simple lobule, crus I, crus II and paramedian lobule), crus I has a peculiar stripe arrangement different from that in other lobules. Climbing fibers projecting to crus I originated from the rostrolateral area in the medial accessory olive and principal olive, while crus I Purkinje cells projected to the ventral area in the interposed and lateral cerebellar nuclei. Regarding single mossy fiber projections, axons originating from the rostral pontine nucleus projected to crus I and often branched to lobule VIb-c, and paraflocculus, whereas axons originating from the central pontine nucleus projected to simple lobule, crus II and paramedian lobule by branching. The results support our hypothesis that rodent crus I is the equivalent of the primate crus I and crus II (Luo et al., Brain Struct Funct, 2017), areas that expand remarkably in dexterous primates or humans in particular, and mainly involved in non-motor function.

Computations in the rabbit's cerebellar flocculus

John I. Simpson
R. A. Hensbroek, J. Maruta, B. J. van Beugen, T. Belton

Department Neuroscience & Physiology, NYU Medical School, New York, United States of America

In the rabbit's flocculus both Type 1 and Type 2 mossy fiber responses to horizontal vestibular rotations are present in about equal numbers. Curiously, the simple spike responses of horizontal Purkinje cells are virtually only Type 2. To address this difference, we recorded from various neuron classes in the anesthetized rabbit's flocculus. Neurons were classified using our previous algorithm (Ruigrok et al., 2011). Of the recorded classes, unipolar brush cells and Golgi cells do not synapse directly on Purkinje cells; their influence is embedded in granule cell activity. Computations were divided into two parts: those occurring through inner paths not synapsing on Purkinje cells and those occurring through outer paths synapsing on Purkinje cells. Type 2 Purkinje cells may arise from dominance of Type 1 molecular layer interneuron (MLI) inhibitory activity in combination with Type 2 granule cell excitatory activity. Similarly, with a different subset of granule cells and MLIs, Purkinje cell activity could be unmodulated, accounting for the near absence of Type 1 Purkinje cells. A general way to comprehend cerebellar computations may be to divide interneuron activity into two anatomically based inner and outer paths, and to then focus on granule cell and MLI diversity.

Input-output organization of posterior vermal and fastigial regions in relation to saccadic eye and head movements

Mayu Takahashi

Department of Systems Neurophysiology, Tokyo Medical and Dental University, Japan

A lesion in the posterior fastigial nucleus (oFN) produces overshoot and undershoot of saccadic eye movements. The purpose of this study was to reveal neural mechanisms of cerebellar eye movement control and understand the pathophysiology of cerebellar movement disorder.

We have shown detailed brainstem neural circuits for horizontal and vertical voluntary saccades. To understand how the cerebellum controls these basic oculomotor circuitries for accurate saccades, we analyzed output pathways from the oFN to brainstem target neurons and input pathways to the oFN in anesthetized cats using electrophysiological and anatomical methods. To search for target neurons of the oFN, we injected dextran-biotin into the oFN and stained axon terminals in the brainstem. Labeled terminals were extensively distributed caudal to the abducens nucleus, but sparsely in its rostral part and were mainly contralateral. Intracellular recording showed that stimulation of the oFN produced strong monosynaptic excitation in neurons of the nucleus reticularis gigantocellularis (NRG), but not of the nucleus reticularis pontis caudalis. Most of these NRG neurons were reticulospinal neurons that projected to cervical motoneurons. However, we could not find fastigial input to inhibitory burst neurons that were assumed to be an oFN target.

Signals for motor control and action prediction in Purkinje cells

Javier F. Medina

Department of Neuroscience, Baylor College of Medicine, Houston, TX, United States of America

To examine the contribution of the cerebellar cortex to motor control and action prediction, we recorded the activity of Purkinje cells during eyeblink conditioning in mice. Mice learned to make anticipatory blinks in response to a predictive cue stimulus that indicated the impending delivery of an aversive airpuff to the eye. We found two types of Purkinje cells with task-related activity: the firing rate of Type I Purkinje cells was suppressed during the production of anticipatory blinks, whereas the firing rate of Type II cells was increased. Histological reconstruction of recording sites revealed that Type I cells are clustered in a previously identified blink-controlling "hotspot" of the cerebellar cortex, while Type II cells can be found more widely distributed in neighboring zones. Analysis of airpuff-driven responses in the two groups of Purkinje cells revealed striking differences in the receptive field organization of their climbing fiber and mossy fiber inputs, suggesting that Type I and Type II cells are specialized for different aspects of predictive motor control.

Neural mechanisms generating cerebellar output in the cerebro-cerebellar communication loop

Takahiro Ishikawa[1]
Saeka Tomatsu[2], Donna S. Hoffman[3,4], Shinji Kakei[1]

[1]Movement Disorders Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, [2]Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan, [3]Department of Neurobiology, [4]Center for the Neural Basis of Cognition, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States of America

The cerebrocerebellum, a part of the cerebellum which forms a looped structure with cortical motor areas, generates output to the cerebral cortex through the dentate nucleus (DN) that is essential for precise limb movements in primates. The question is how DN cells generate strong burst activity, given the intensive inhibitory drive from Purkinje cells (PCs). There are two excitatory inputs to DN, mossy fiber (MF) and climbing fiber collaterals, but neither of them appears to have sufficient strength to generate burst activity in DN. Two possible mechanisms remain: post-inhibitory rebound excitation or disinhibition. If rebound excitation works, phasic excitation of PCs and a concomitant inhibition of DN cells should precede excitation of DN cells. On the other hand, if disinhibition plays a primary role, phasic suppression of PCs and activation of DN cells should be observed at the same timing. We examined unit activity of MFs, PCs and DN cells during step-tracking wrist movements in Japanese monkeys, and found that burst activity in DN cells is generated by reduced inhibition from PCs, i.e., by disinhibition. This result indicates that suppression of PCs, which has been considered secondary to facilitation, plays the primary role in generating outputs from the cerebrocerebellum.

The Basal Ganglia and the Cerebellum: Nodes in an Integrated Network.

Peter L. Strick

Thomas Detre Professor & Chair of Neurobiology, Scientific Director, University of Pittsburgh Brain Institute, University of Pittsburgh, United States of America

The basal ganglia and the cerebellum are considered to be distinct subcortical systems that perform unique functional operations. The outputs of the basal ganglia and the cerebellum influence many of the same cortical areas, but do so by projecting to distinct thalamic nuclei. As a consequence, the two subcortical systems were thought to be independent and communicate only at the level of the cerebral cortex. This presentation will review recent data demonstrating that the basal ganglia and the cerebellum are interconnected at the subcortical level. The subthalamic nucleus in the basal ganglia is the source of a dense di-synaptic projection to the cerebellar cortex. Similarly, the dentate nucleus in the cerebellum is the source of a dense di-synaptic projection to the striatum. These observations lead to a new functional perspective that the basal ganglia, the cerebellum, and the cerebral cortex form an integrated network. This network is topographically organized so that the motor, cognitive, and affective territories of each node in the network are interconnected. This perspective explains how synaptic modifications or abnormal activity at one node can have network-wide effects. A future challenge is to define how the unique learning mechanisms at each network node interact to improve performance.

Roles of subcortical preparatory signals in self-timing

Masaki Tanaka

Department of Physiology, Hokkaido University, Japan

The ability to flexibly adjust movement timing is important for everyday life. Although the preparatory activity reported in the cerebellum, the basal ganglia and the frontal cortex are likely to play crucial roles, the underlying mechanism remains unclear. To understand this, we examined neuronal activity in monkeys generating a self-initiated saccade at instructed timing following a visual cue. We found that neurons in the cerebellar dentate nucleus exhibited preparatory activity during ~500 ms before self-timed saccades irrespective of delay interval, while those in the caudate nucleus showed ramping activity throughout the delay period. In contrast, neuronal correlates of trial-by-trial variation of self-timing emerged earlier in the cerebellum than the striatum. Thus, during adjustment of movement timing, two distinct subcortical signals appear to exist, each of which reflects 1) stochastic variation of subjective timing and 2) the instructed interval timing. The stochastic timing correlated with pupil diameter before monitoring of time, while the instructed timing correlated with visual response gain and low frequency power of local field potentials in the striatum. The preparatory activity in the cerebellum may play a role in fine adjustment of self-timing, while that in the striatum may keep track of elapsed time for generating timely movements.

Neural substrates of cerebrocerebellar loop

Yoshikazu Shinoda

Department of Systems Neurophysiology, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Cerebrocerebellar loop is one of the most important structures for control of voluntary movements. The connections from the cerebellar nuclei to the motor corticies and its reverse connections from the cerebral cortex to the cerebellar nuclei have been extensively investigated both electrophysiologically and anatomically.

This study tried to reveal characteristic features of synaptic connections of cerebrocerebellar loop and axonal mophologies of its constituent neurons. Synaptic nature of input from the cerebellar nucleus to thalamocortical neurons and pyramidal neurons in the cortex was analyzed using an intracellular recording technique in anesthetized cats. By injecting horseradish peroxidase into single penetrated axons after electrophysiological identification, entire axonal trajectories of single stained cerebellar output neurons and thalamocortical neurons were visualized with three dimensional reconstruction of serial sections. Cerebral input from the motor cortex to cerebellar neurons and axonal morphologies of their constituent neurons were analyzed in a similar way. In addition, detailed projection patterns of single mossy fibers of pontine nucleus neurons were analyzed in the rat. Based on these analyses, I will discuss the functional neural circuits to generate the final output from the cerebellar nucleus to its target for control of movement.

How the cerebellum can help us the way we think

Chris I. De Zeeuw

Netherlands Institute of Neuroscience, Royal Dutch Academy of Arts and Sciences, the Netherlands

The brain can store information in neural activity to remember past events and plan future behavior. Ramping activity in cortex reflects anticipation of specific movements. This preparatory activity has been postulated to emerge from processes distributed across multiple brain regions, but it has remained unclear how this activity is mediated by multi-regional interactions and which brain areas are involved. For this lecture, I will describe how a persistent representation of information in cortex depends on cerebellar processing, a structure thought to be primarily involved in control of movement. During a sensory discrimination task, in which mice use short-term memory to plan a future directional movement, they show persistent ramping activity in both their cortex and cerebellum, instructing movements seconds before their onset. Transient perturbations in cerebellar nuclei activity disrupt these ramping activities as well as their choices to move their tongue in the right direction. Moreover, silencing cortex activity abolishes preparatory activity in the cerebellar nuclei affecting a closed loop. Finally, ongoing motor programs in this closed loop can be altered by manipulating activity in the olivocerebellar system, resetting the planned behavior. These experiments highlight the way the cerebellum can control cognitive behaviors that extend beyond coordination of ongoing movements.

Involvement of cerebello-cerebral functional networks and cognitive decline in multiple system atrophy

Hirohisa Watanabe, Gen Sobue

Nagoya University Graduate School of Medicine, Brain and Mind Research Center, Japan

The cerebellum plays a role for movement and cognition. We previously showed the relationship between cerebellar atrophy and frontal involvement, and also cognitive dysfunction in patients with multiple system atrophy (MSA) (Neurology 2008, J Neurol 2018). However, it remains unclear how cerebellar degeneration influences on the cognitive function particularly through alterations of cerebello-cerebral networks composed of polysynaptic connectivity. Resting-state functional MRI (rsfMRI) can provide the information of polysynaptic anatomical pathways including the cerebellar network. Thus, we investigated 32 probable MSA patients and 32 healthy controls using independent component analysis (ICA) and dual-regression analysis related to the cerebellum. In the MSA group, a wide range of cerebellar volume loss was observed. ICA and dual-regression analysis showed lower functional connectivity (FC) regions located in the cerebellum of the left executive control and salience networks. Seed-based analysis based on these lower FC regions showed that cerebello-cerebral networks were extensively disrupted. Furthermore, global cognitive measures correlated with FC between the right lobules VI/Crus I corresponding to left executive control network and the medial prefrontal/anterior cingulate cortices and amygdala/hippocampal gyrus. These results indicate that decreased cerebello-cerebral FC can be associated with cognitive decline in MSA.

The three cornerstones of cerebellar ataxia

Mario Manto

Service des Neurosciences, Université de Mons, Belgium. / Service de Neurologie, CHU-Charleroi, Belgium

Historically, the terminology of cerebellar ataxia was coined to designate motor deficits of the limbs observed in patients with cerebellar lesion. The list of symptoms and signs has expanded and includes now both oculomotor deficits and deficits related to linguistic, cognitive and affective functions. The cerebellar deficits encompass a range of symptoms initially thought to be of extra-cerebellar origin. The classification of the cerebellar deficits into a cerebellar motor syndrome (CMS), a vestibulo-cerebellar syndrome (VCS) and Schmahmann's syndrome (CCAS : cerebellar cognitive affective syndrome) is justified not only on a clinical basis, but also on neuroanatomical findings. The cerebellum is organized into (1) a primary sensorimotor region in the anterior lobe (lobules I-V) with adjacent part of lobule VI and a second sensorimotor region in lobule VIII, (b) vestibulo-cerebellar areas (lobules V-VII, IX-X) gathering the flocculus-paraflocculus, the nodulus-ventral uvula and the dorsal oculomotor vermis (lobules V-VII), and (c) cognitive and limbic regions located in the posterior lobe (lobule VI, lobule VIIA which includes crus I and crus II, and lobule VIIB). The limbic cerebellum is mainly represented in the posterior vermis. The cortico-ponto-cerebellar and cerebello-thalamocortical loops establish close functional connections between the cerebellum and the supratentorial motor, paralimbic and association cortices, and cerebellar symptoms are associated with an impairment of these loops.

Learning from the past: a reverberation of past errors in the cerebellar climbing fiber signal

Peter Thier

Department of Cognitive Neurology, Hertie Institute of Clinical Brain Research, University of Tübingen, Germany

The cerebellum allows us to rapidly adjust motor behavior to the needs of the situation. It is commonly assumed that cerebellum-based motor learning is guided by the difference between the desired and the actual behavior, i.e. by error information. Not only immediate but also future behavior will benefit from an error because it induces lasting changes of parallel fiber synapses on Purkinje cells (PC), whose output mediates the behavioral adjustments. Olivary climbing fibers, likewise connecting with PC, are thought to transport information on instant errors, needed for the synaptic modification, yet not to contribute to error memory. Here we report work on monkeys, tested in a saccadic learning paradigm that challenges this concept. We demonstrate not only a clear CS signature of the error at the time of its occurrence, but also a reverberation of this signature much later, before a new manifestation of the behavior, suitable to improve it.

Population coding in the cerebellum

Reza Shadmehr

Biomedical Engineering, Johns Hopkins University, United States of America

The cerebellum is responsible for making accurate predictions about sensory consequences of actions. However, it has been difficult to understand how its principal cells, Purkinje cells, represent this prediction, and how that prediction is then changed following experience of error. Here, I will summarize data from recent experiments that have suggested a solution to this problem. It appears that the key is the special anatomical organization of the Purkinje cells, which appear to form small cluster, wherein the membership in the cluster is specified by the cell's preference for error. The result is an interesting internal organization of a neural network that not only learns from its prediction errors, but is empowered to reduce those errors through downstream projections onto effectors.

Reward signalling in cerebellar cortex

Michael Häusser

Professor of Neuroscience, University College London, United Kingdom

There is increasing evidence for the role of the cerebellar cortex in cognitive processing, but the specific input pathways conveying this information remain unclear. The climbing fiber connection with Purkinje cells, one of the most powerful synaptic inputs in the brain, has traditionally been thought to process the direct relationships between sensation and action. I will describe work probing the role of the cerebellar climbing fiber system in generating predictions about and evaluating the outcome of learned associations between motor actions, sensory stimuli, and upcoming reward, using 2-photon imaging in mice performing a novel behavioural paradigm in which they receive rewards under conditions of varying predictability in a virtual reality environment. Our results reveal that climbing fibers can encode non-sensorimotor parameters during learned associative behaviour, and allow us identify a specific input pathway for the cerebellar contributions to reward signaling.

Error signals in the cerebral cortex, the red nucleus and the cerebellum that drive adaptation in reaching

Shigeru Kitazawa

Graduate School of Frontier Biosciences, Osaka University /
Graduate School of Medicine, Osaka University /
Center for Information and Neural Networks (CiNet), Osaka University, Japan

Motor control of reaching is so adjusted every time we reach to null the end-point error. The cerebellum has been implicated for the process and the error information is encoded by the climbing fiber signals. To elucidate the origins of information, we recorded neural activities in parietal areas 5 and 7, the premotor and primary motor cortices (PM and M1), and the red nucleus in monkeys. We found that all regions encoded error information with a peak latency between 100 and 200 ms. Post-movement microstimulation to these areas except area 7 induced trial-by-trial increases in reach errors in the direction that would cancel the preferred error at each location. The induced errors subsided gradually as in ordinary adaptation. We further examined if area 5 and 7 neurons respond to errors due to a target jump. Interestingly, area 7 neurons alone responded to a target-jump. Further, stimulation to area 7 induced adaptation to compensate for the target-jump error. We speculate that the parietal regions discriminate between causes of error, and the motor error component is shared with the PM, and M1, combined in the red nucleus and the inferior olivary nuclei, and provided to the cerebellum to null the end-point error.

Purkinje cell error and kinematic representations in cerebellar-dependent motor behaviors

Timothy J. Ebner

Department of Neuroscience, University of Minnesota, United States of America

Fundamental for understanding cerebellar function is determining the representations in the activity of Purkinje cells, the sole output of the cerebellar cortex. A central question, and the focus of this talk, is the nature of the information represented and the interactions between the low frequency complex spike discharge and the high frequency simple spike firing of Purkinje cells. Although error processing has been ascribed to climbing fiber input, Purkinje cell simple spike discharge provides exquisite continuous error and kinematic signals that both lead and lag movements, suggesting that Purkinje cells encode not only feedback but also predictions of upcoming motor behavior and performance. Manipulations of the visual feedback show that Purkinje cell discharge carries both the motor predictions and sensory feedback required to implement a forward model. Further, complex spike discharge is not limited to signaling errors, can be predictive and dynamically controls the information in the simple spike firing to meet the demands of upcoming behavior. Overall, these rich and unexpected representations highlight the need to revisit existing dogmas about simple spike and complex spike discharge. Therefore, integrating established and newer findings, we propose the dynamic encoding hypothesis for the action of complex spikes on Purkinje cell information processing.

Distributed population coding by cerebellar complex spikes

Takayuki Michikawa

Biotechnological Optics Research Team, RIKEN Center for Advanced Photonics, Japan

The input from a climbing fiber originated from the inferior olive elicits a complex spike in a Purkinje cell in the cerebellum. Although the inferior olive receives massive sensory inputs, its encoding mechanism is largely unknown. Here I optically measured complex spikes from over 10,000 Purkinje cells simultaneously and discovered that the dorsal surface of the mouse cerebellar cortex was divided into approximately 200 segments based on complex spike synchrony. Stimulation of four limb muscles each evoked excitatory or inhibitory complex spike responses in nearly all segments. Bayesian decoding showed that ensemble patterns of segmental complex spike activity encoded the stimulation onset time and target muscle moment-by-moment, leading to propose that distributed population coding is the basis for information transfer in the olivocerebellar system.

Delving more deeply into the details of cerebellar learning

Stephen G. Lisberger
Nathan J. Hall, David J. Herzfeld

Department of Neurobiology, Duke University School of Medicine, Durham, NC, United States of America

In smooth pursuit eye movements, climbing fiber inputs to the floccular complex provide error signals when an instructive target motion causes visual image motion. If a complex spike occurs in a Purkinje cell on one learning trial, then that cell's simple-spike firing expresses a properly-timed, learned depression on the next trial. Thus, the climbing fiber input is a primary cause of learning at the parallel fiber to Purkinje cell synapse. However, learning blocks that consist of up to 1,000 trials reveal multiple time courses of learning and suggest a second component of learning that could occur at a different site. Analysis of the expression of learning after a single instructive target motion reveals larger expression of learning whenever eye speed is faster during the initiation of pursuit, implying that parallel fibers represent eye velocity and suggesting that Golgi cell feedback differentiates eye position mossy fiber inputs. The effects of eye speed on the expression of learning are quite different after many learning trials, consistent with a transfer of learning to another site. We conclude that the original cerebellar learning theory is true, but that it is part of a richer and more nuanced learning system.

New approaches to old problems to understand cerebellar LTD/LTP

Michisuke Yuzaki

Department of Physiology, Keio University School of Medicine, Tokyo, Japan

Long-term potentiation (LTP) and depression (LTD) of AMPA-type glutamate receptor (AMPAR)-mediated synaptic transmission have been proposed as a cellular substrate for learning and memory. Activity-induced AMPAR exocytosis and endocytosis at postsynaptic membranes are believed to underlie LTP and LTD, respectively. However, it remains largely unclear whether LTP/LTD and AMPAR trafficking at specific synapses are causally linked to learning and memory *in vivo*. Cerebellar LTP and LTD at parallel fiber-Purkinje cell synapses were originally proposed as a basis of the motor learning by Marr (1969) and Albus (1971), respectively. While Ito and colleagues subsequently showed that it was LTD that mediated motor learning underlying visual adaptation of the horizontal optokinetic response and vestibulo-ocular reflex, de Zeeuw and colleagues have recently provided experimental evidence indicating that LTP at these synapses serves as a substrate for motor learning. In addition, although induction of both LTP and LTD at these synapses require NMDA-type glutamate receptor (NMDAR) activation, it has remained unclear how NMDAR mediate bidirectional synaptic plasticity. To address these old but important questions, we have recently developed new tools. In this talk, I would like to discuss our recent findings on LTP/LTD mechanisms in the cerebellum using these tools.

Role of cerebellum in acquisition and consolidation of memory of motor learning

Soichi Nagao

Laboratory for Integrative Brain Functions, Nozomi Hospital, Ina, Saitama, Japan

The crucial role of cerebellum in motor learning has been revealed by experiments using adaptation of horizontal optokinetic response (HOKR) and vestibulo-ocular reflex (HVOR). The cerebellar flocculus Purkinje cells receive optokinetic and vestibular inputs through mossy-parallel and climbing fibers and issue their outputs directly to the vestibular nuclear neurons (VN) that drive HOKR/HVOR. Gains of HOKR/HVOR are quantified by the magnitudes of evoked eye movements vs. those of optokinetic/vestibular stimulation. One-hour of optokinetic/vestibular training, which induces sufficient amount of retinal slips, adaptively modify HOKR/HVOR gains through the plasticity of parallel fiber-Purkinje cell synapses. Although the memory of adaptation formed by 1-h training decays within one day, repetitions of daily 1-h training further largely modify HOKR/HVOR gains for weeks through the plasticity of mossy fiber-VN synapses. Thus, the memory of adaptation is initially formed at flocculus Purkinje cell synapses and later transferred to VN synapses for consolidation. I present lines of experimental evidence which support this view and discuss on the possible neural mechanisms underlying the memory transfer by referring to our gene-knockout mice experiments.

Contribution of excitatory and inhibitory synaptic plasticity in a Purkinje neuron to oculomotor learning paradigms

Tomoo Hirano

Department of Biophysics, Graduate School of Science, Kyoto University, Japan

Long-term depression (LTD) at parallel fibers (PF) to a Purkinje neuron (PN) synapses has been considered to contribute to motor learning, although conflicting results have also been reported. We have addressed this issue by examining PF-PN synaptic properties after establishment of motor learning. The averaged amplitude of quantal excitatory postsynaptic currents (EPSCs) became smaller and LTD induction was suppressed at PF-PN synapses after continuous optokinetic stimulation inducing adaptation of optokinetic response, which suggests that LTD occurs during motor learning and is nearly saturated. If so, why LTD suppression sometimes fails to affect motor learning? We considered that other plasticity mechanisms might also contribute to motor learning and compensate for defects of LTD. We found that transgenic mice deficient in rebound potentiation (RP), a type of synaptic plasticity at inhibitory interneurons to a PN synapses, show defective motor learning. LTD is depression of excitatory synaptic transmission and RP is potentiation on inhibitory synaptic transmission onto a PN. Induction of both LTD and RP depends on the climbing fiber activity and on the increase in intracellular Ca^{2+} concentration of a PN. Thus, they could occur simultaneously and work synergistically.

Temporal memory in cerebellar Purkinje cells

Germund Hesslow

Associative Learning Group, Department of Experimental Medical Science, Lund University, Sweden

A popular idea, associated with Cajal and Hebb, is that learning consists in strengthening or weakening of synaptic transmission. Long term potentiation and depression (LTP and LTD) are well documented phenomena and evidence by Ito and others suggests that they are important for motor learning in the cerebellum. A problem with LTP/LTD is that it cannot readily account for timing of neural responses. An example is Pavlovian eyeblink conditioning where pairings of tone and air puff to the eye causes acquisition of a conditional blink that is adaptively timed. The learning occurs in the cerebellum where timed pauses in Purkinje cell firing drive the overt behaviour. If LTD was the learning mechanism, the timing would require a temporal code in the input signals to the cell, due to various delays. LTD of synapses that are active at the right time could then results in appropriately timed responses. Results from our lab show that timing of Purkinje cell pauses does not depend on temporal information in the input and suggest instead that the temporal memory is stored within the cell by a novel mechanism.

Heterogeneity of cerebellar plasticity rules

Jennifer L Raymond

Department of Neurobiology, Stanford School of Medicine, United States of America

The research in my lab investigates the algorithm the cerebellar circuit uses to learn. This algorithm is defined by the rules governing the local "decisions" each synapse makes on a moment-by-moment basis about whether to alter its strength, based on its pattern of input. I will describe recent progress we have made in understanding synaptic learning rules in the cerebellum. Neuroscientists have generally viewed learning as being implemented by a few, generic synaptic plasticity rules, with the specialization for specific behavioral tasks arising from the circuit architecture. In contrast, we recently discovered that the synaptic plasticity rules themselves can be precisely tuned to functional requirements.

Mechanisms of long-term synaptic plasticity in the cerebellar Purkinje cell

Kazuhiko Yamaguchi

Laboratory for Behavioral Genetics, CBS RIKEN, Japan

Understanding of exact molecular mechanism of the synaptic plasticity is crucial to identify "engram" in the brain. At the parallel fiber (PF)-Purkinje cell (PC) synapse in the cerebellum, though time-dependent control of exo/endocytosis and lateral mobility of AMPA-type glutamate receptors (AMPA-Rs) are supposed to be important to determine synaptic strength and its plasticity, realistic kinetic parameters of AMPAR-trafficking and their changes underlying synaptic plasticity were not experimentally measured. Here, we measured a rate-constant of endocytosis of AMPA-Rs using a caged inhibitory peptide, and compared it before and after LTD induction. Caged peptide, of which original form blocked exocytic insertion of GluA2-containing AMPA-Rs into synapse, was applied to PC in rat cerebellar slice. Measured rate-constant of endocytosis of AMPA-R was 0.8 min^{-1}. Constitutive exocytosis of AMPA-R was equilibrated with this endocytosis. Estimated amount of destabilization of AMPA-Rs at LTD was insufficient to explain LTD, thus further mechanism was required. Endocytic rate was not affected upon LTD, but exocytic insertion was markedly suppressed during LTD, suggesting that partial loss of recycling pool of AMPA-Rs was a long-lasting mechanism of LTD.

Perineuronal nets in the deep cerebellar nuclei regulate GABAergic transmission and delay eyeblink conditioning

Moritoshi Hirono[1,2]
Satoshi Watanabe[3], Fuyuki Karube[4], Fumino Fujiyama[4], Shigenori Kawahara[5], Soichi Nagao[2,6], Yuchio Yanagawa[7], Hiroaki Misonou[1]

[1]Laboratory of Ion Channel Pathophysiology, Graduate School of Brain Science, Doshisha University, Kyoto, Japan, [2]Laboratory for Motor Learning Control, RIKEN BSI, Wako, Japan, [3]National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan, [4]Laboratory of Neural Circuitry, Graduate School of Brain Science, Doshisha University, Kyoto, Japan, [5]Graduate School of Science and Engineering, University of Toyama, Toyama, Japan, [6]Laboratory for Integrative Brain Functions, Nozomi Hospital, Ina, Japan, [7]Department of Genetic and Behavioral Neuroscience, Gunma University Graduate School of Medicine, Maebashi, Japan

To understand information processing in the cerebellar circuit for motor coordination and learning, it is important to identify the mechanisms regulating GABAergic transmission onto neurons in the deep cerebellar nuclei (DCN). Perineuronal nets (PNNs) are the extracellular matrix of CNS neurons and regulate brain functions. Although PNNs are known to enwrap DCN neurons, the role of PNNs in cerebellar functions remains unknown. We found that PNN depletion by chondroitinase ABC in the mouse DCN increased the amplitude of evoked inhibitory postsynaptic currents (IPSCs) recorded from DCN neurons and reduced their paired-pulse ratios. ChABC treatment also increased the miniature IPSC frequency without changing the amplitude or the density of PC terminals, suggesting that PNN depletion enhances GABA release from presynaptic terminals. Mice having received the enzyme in the interpositus nuclei exhibited a higher conditioned response rate in delay eyeblink conditioning than control mice. These results suggest that PNNs of the DCN regulate presynaptic functions of Purkinje cell terminals and functional plasticity of synapses on DCN neurons, which influences the flexibility of adult cerebellar functions.

The cerebellum as a predictor in movement and cognition.

R. Chris Miall

Behavioural Brain Sciences, School of Psychology, University of Birmingham, Edgbaston, Birmingham, United Kingdom

I will present a short summary of my research into the contribution of the cerebellum to motor control and coordination, and suggest that the most plausible single operation it performs is short term prediction. These predictions are vital in the sensorimotor domain, and may have many other uses, including in cognitive operations. I will therefore also present more recent data from studies of language prediction. I will end with some speculation about the links between the cerebellum and and the basal ganglia, and introduce current work exploring the possibility of using a new form of MEG to record cerebellar signals, that might allow tests of predictive processing in cognitive tasks.

Cerebellar role in predictive control of eye movement in fish and humans.

Yutaka Hirata

Neural Cybernetics Laboratory, Department Robotics Science and Technology, Chubu University College of Engineering, Japan

Predictive motor control is necessary as sensory feedback loops usually add significant delays that are too long to compensate for rapid and high frequency components of motor errors and may cause unstable oscillatory motor output. Predictive eye movement control was first demonstrated in goldfish (Marsh and Baker, 1997): After prolonged presentation of a periodic optokinetic visual stimulation eye velocity starts to decrease before a change in direction of the same stimulus. When the visual stimulation period is suddenly elongated, eye velocity starts to decrease around the timing of the change in direction of the training stimulus. When the light is turned off, eye velocity continues to respond in the dark as if the training stimulation is still present. We have demonstrated recently that carps acquire this predictive optokinetic eye velocity control while zebrafish and medaka do not. We have also shown that some human subjects acquire similar predictive optokinetic response while others do not. Examining the capacity of velocity storage mechanism in fish and humans as well as conducting single unit recordings from vestibulo-cerebellar Purkinje cells and cerebellectomy in goldfish, we argue how the cerebellum learns to predict when to start and when to stop the eyes.

Contribution of internal models on sensorimotor control

Hiroaki Gomi

NTT Communication Science Laboratories, Japan

Pioneer studies of computational aspects of the cerebellum function proposed adaptation models, and further studies have formalized computational schemes using internal models for movement controls. In this talk, I will first stress an importance of knowledge of dynamics in the motor control. Although several model-based reasoning proposed that the movement can be achieved without an explicit knowledge of object dynamics, our experimental examinations of arm movement control have shown that the arm dynamics should be certainly considered in producing motor commands for smooth movements.

In addition to this fundamental requirement, on the bases of one of internal model control schemes, we analyzed the simple and complex spike activities in the cerebellum VPFL during ocular-following-response, using linear dynamics model. Since estimated parameters by a regression analysis of the simple spike well represented the eye-ball dynamics and both of simple and complex spike activities were well reconstructed (in a mirror manner) by the eye acceleration and velocity, we concluded that the dynamic component of the eye response is coordinated by the VPFL.

We also considered the estimation of dynamic component in perception. Experimental results indicate that resistive somatic sensation caused by a delayed visual feedback of our hand is not caused by the positional difference of predicted and current states, rather is caused by the interaction-force estimation from the visual motion of an object. These lines of evidence suggest that, in addition to the prediction by the forward model, the inverse computation is also employed in the brain computation for motor interaction with environments.

Neural evidence of the cerebellum as a state predictor

Hirokazu Tanaka

Japan Advanced Institute of Science and Technology, Japan

This talk provides neural evidence that the cerebellar circuit can predict future inputs from present outputs, a hallmark of an internal forward model. Recent computational studies hypothesize that the cerebellum performs state prediction known as a forward model. To test the forward-model hypothesis, I analyzed activities of 94 mossy fibers (inputs to the cerebellar cortex), 83 Purkinje cells (output from the cerebellar cortex to dentate nucleus), and 73 dentate nucleus cells (cerebellar output) in the cerebrocerebellum, all recorded from a monkey performing step-tracking movements of the right wrist. I found that the firing rates of one population could be reconstructed as a weighted linear sum of those of preceding populations. In addition, the firing rates of mossy fibers at time t+t1 could be well reconstructed from as a weighted sum of firing rates of dentate cells at time t, thereby proving that the dentate activities contained predictive information about the future inputs. The linear equations derived from the firing rates resembled those of a predictor known as Kalman filter composed of prediction and filtering steps. This analysis of cerebellar activities supports the forward-model hypothesis of the cerebellum.

Computer simulation of a monkey-scale cerebellum with 8 billion spiking neurons in realtime and its applications

Tadashi Yamazaki

Graduate School of Informatics and Engineering, The University of Electro-Communications, Tokyo, Japan

The computational power of supercomputers has been increasing exponentially. By 2022, the peak performance will reach to 1 exaflops. When an exaflops machine is built, we will be able to simulate an entire human brain on the supercomputer. At present, we have built a large-scale spiking network model of the cerebellum on Gyoukou, a supercomputer with the peak performance of 28.19 petaflops built by PEZY Computing/ExaScaler. The model comprises more than 8 billion neurons, and the size is comparable with the cerebella of two monkeys. The computer simulation runs in realtime. Synaptic plasticity at parallel fibers is implemented, so that the model can perform online learning. We confirmed its basic dynamics and learning capacity by computer simulation of gain adaptation of optokinetic response eye movements. Meanwhile, we have proposed a theory in that the cerebellar cortex is a reinforcement learning machine, in contrast to the standard Marr-Albus-Ito model. Owing to its repetitive anatomical structure, the cerebellum could be considered a collection of a number of reinforcement learning modules. Thus, our artificial cerebellum will be used as a massively parallel reinforcement learning machine for machine learning and for solving real world problems.

Systems neuroscience and clinical neurology of cerebellar cognition

Jeremy D. Schmahmann

Professor of Neurology, Harvard Medical School / Founding Director, Ataxia Unit / Cognitive Behavioral Neurology Unit / Director, Laboratory for Neuroanatomy and Cerebellar Neurobiology / Department of Neurology, Massachusetts General Hospital and Harvard Medical School, United States of America

Cerebellar neuroscience has undergone a paradigm shift. The theories of the universal cerebellar transform, dysmetria of thought, and the principles of organization of cerebral cortical connections, together with brain imaging studies and clinical evidence, have recontextualized the cerebellum as a critical node in the distributed neural circuits subserving behavior. Confirmation of primary and secondary sensorimotor cerebellar representations linked with spinal cord, and identification of three representations of cognition in the posterior lobe linked with cerebral association areas, provide the framework for cerebellar cognition. Lesions of the anterior lobe primary sensorimotor representations produce dysmetria of movement - the cerebellar motor syndrome; lesions of the posterior lobe cognitive-emotional cerebellum produce dysmetria of thought and emotion - the cerebellar cognitive affective / Schmahmann syndrome. The recognition that the cerebellum does to thought and emotion what it does to motor control advances the understanding of the mechanisms of cognition, and opens new therapeutic opportunities in neuropsychiatry. This lecture will provide an overview of the recent findings in cerebellar cognitive neuroscience in the lab and in the clinic. It will conclude with a presentation of the validated cerebellar cognitive affective / Schmahmann syndrome scale for the detection and rating of cognitive impairment in patients with cerebellar disorders.

The cerebellum and autism: From structure to function

Catherine J. Stoodley

Associate Professor, Psychology Director, Undergraduate Program in Neuroscience, American University, Washington, DC, United States of America

Differences in cerebellar structure and function are well-documented in autism spectrum disorders (ASD). Through both meta-analytic and prospective studies, we have identified several structural differences within the cerebellum in ASD, including reduced grey matter in right lobule VII. Several lines of evidence suggest that right lobule VII may play an important role in the etiology of ASD: this region is engaged in social cognition in typically-developing individuals; right lobule VII is part of neural circuits that are dysfunctional in ASD, such as the default mode network; inhibition of right lobule VII in rodent models is sufficient to produce ASD-like behaviors; and excitation of this region rescued social deficits in a mouse model of ASD. Our recent work investigates the functional significance of this region in ASD using neuromodulation and neuroimaging in both typically-developing adults and adults with ASD. These findings will be discussed within a developmental framework, with reference to potential mechanism(s) by which early cerebellar dysfunction might impact ASD-relevant behaviors.

Prism adaptation test: A practical and quantitative method to evaluate cerebellar function

Hidehiro Mizusawa

National Center of Neurology and Psychiatry, Japan / Tokyo Medical and Dental University, Japan

Diagnosis of cerebellar disorders depends on neurological examination by trained neurologists. Cerebellar signs including ataxia were usually evaluated by scales such as ICARS and SARA, which appear hard to detect mild changes of slowly progressive neurodegenerative diseases. We need a good quantitative methods evaluating cerebellar functions among which motor learning is a cardinal feature with a long history of researches in neurophysiology. We thought prism adaptation using finger-reach movement to a target on a touchscreen may be a good task because adaptation time is fairly short among many tasks. The whole test was composed of 3 consecutive sessions: 1) 50 trials with normal vision (BASELINE), 2) 100 trials with prism (PRISM) and 3) 50 trials without prism (REMOVAL). Adaptation index (AI) was calculated by multiplying each probability of acquisition in the last 10 trials of PRISM, retention in the initial 5 trials of REMOVAL and extinction of in the last 10 trials of REMOVAL. AI clearly distinguished patients with cerebellar ataxia from normal controls and was significantly correlated with SARA. This system is compact and available at outpatient clinics and useful for quantitative evaluation of the cerebellar function in clinical trials.

Single strand DNA break repair and ataxias: lesson from Ataxia with oculomotor apraxia 1 / Early-onset ataxia with ocular motor apraxia and hypoalbuminemia (AOA1/EAOH)

Osamu Onodera
Masayoshi Tada, Akio Yokoseki

Department of Neurology, Clinical Neuroscience Branch, Brain Research Institute, Niigata University, Japan

DNA single strand breaks (SSBs) are discontinuities in one strand of DNA duplexes and can occur much more frequently than DNA double-strand breaks in cells. Recently repair disorders of SSB have been noted to cause neurodegenerative disorders including early onset ataxia with ocular motor apraxia and hypoalbuminemia (AOA1/EAOH). AOA1/EAOH is characterized by early onset ataxia, ocular motor apraxia, severe peripheral neuropathy, and hypoalbuminemia. Involuntary movements and psychiatric disorders are often observed. Neuropathological features are severe loss of Purkinje cells and moderate neuronal loss at the dorsal root ganglion and anterior horn. AOAl / EAOH is caused by mutation of the APTX gene encoding the aprataxin protein which is a member of the histidine triad superfamily of nucleotide hydrolase/transferase. Aprataxin contributes to single-strand break repair. Therefore, AOA1 / EAOH is thought to be caused by an accumulation of SSB. In my lecture, I will introduce the clinical symptoms of AOA 1 / EAOH and the function of aprataxin, and I would like to discuss why some neurons are vulnerable to SSB.

Essential Tremor and the Cerebellum

Sheng-Han Kuo

Department of Neurology, Columbia University, United States of America

The cerebellum has been implicated in essential tremor (ET) based on the clinical, neuroimaging, and neuropathological studies; however, how the cerebellum can generate rhythmic movements (i.e. tremor) remains poorly understood. To find the cause of tremor, an extensive search for structural changes in the postmortem ET cerebellum has been performed, which identifies alterations of Purkinje cell (PC) morphology, including moderate PC loss, PC axonal torpedoes, and abnormal PC synaptic organization. Among these pathological changes, abnormal PC synaptic organization appears to be specific in ET and occurs across different ET subtypes regardless of age of tremor onset and the family history of tremor. To further understand how abnormal PC synaptic organization can lead to tremor, a mouse model with similar abnormal PC synaptic organization has been established, and this mouse model develops ET-like tremor, indicating the instrumental role of PC synapses in kinetic tremor generation. Collectively, the combination of human neuropathology and animal models provides an important platform to study tremor disorders and advances our understanding the role of cerebellum in ET.

Cerebellar reserve and immune-mediated cerebellar ataxias

Hiroshi Mitoma[1]
Mario Manto[2]

[1]Department of Medical Education, Tokyo Medical University, Tokyo, Japan, [2]Service de Neurologie, Médiathèque Jean Jacquy, CHU-Charleroi, and Service des Neurosciences, University of Mons, Belgium

Immune-mediated neuronal dysfunction is one key-pathomechanism of cerebellar ataxias (CAs). Immune-mediated cerebellar ataxias (IMCAs) include gluten ataxia, paraneoplastic cerebellar degenerations, post-infectious cerebellitis, and anti-GAD65 antibody associated CA. IMCAs share common features with regard to therapeutic approaches. When certain factors trigger immune processes, elimination of the antigen becomes a priority. Furthermore, various immunotherapeutic modalities (e.g., steroids, immunoglobulins, plasmapheresis, immunosuppressants, rituximab) should be considered alone or in combination to prevent the progression of the IMCAs. Treatment introduced at an early stage, when CAs or cerebellar atrophy is mild, is associated with better prognosis.

Functional disorders might proceeds cell death in IMCAs. For example, recent physiological studies in vitro and in vivo have elucidated that binding of GAD65 by anti-GAD65 Abs elicits loss of GAD65 functions pertaining GABA release with an epitope dependence, leading to the development of CAs.

In conclusion, preservation of the "cerebellar reserve" is necessary for improvement of CAs and resilience of the cerebellar networks. In this regard, we emphasize the therapeutic principle of "Time is Cerebellum" in IMCAs.

Molecular pathogenesis of SCA6 and SCA31

Kinya Ishikawa

Department of Neurology and Neurological Science / Department of Personalized Genomic Medicine for Health, Tokyo Medical and Dental University, Japan

Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant neurodegenerative disease caused by a tri-nucleotide CAG repeat expansion in the last exon of the α1A voltage-dependent calcium channel gene in chromosome 19p. SCA31 is also an autosomal dominant neurodegenerative disease caused by a penta-nucleotide including (TGGAA) repeat in the intron shared by two genes BEAN-1 and TK2 lying in human chromosome 16q. These diseases usually show pure cerebellar syndrome. The Purkinje cell (PC) in the cerebellar cortex is most heavily affected than any other neurons in the brain. Regarding the pathogenesis of SCA6, two different mechanisms are considered: one is an accumulation of calcium channel protein in the cytoplasm of PC, and the other is an entry of a short fragment of calcium channel in the nucleus of PC affecting transcriptional dysregulations. In SCA31, it is plausible that the penta-nucleotide TGGAA repeat transcribed into UGGAA repeat leads to PC degeneration. We have identified a number of (UGGAA)-binding proteins including TDP-43, which have diverse biological functions such as RNA transport, splicing and editing. Studying these two distinct diseases are important to understand biology of Purkinje cells. Recent progresses in understanding these two diseases will be presented.

Tandem Internal Models Fulfill Precise Motor Control

Takeru Honda

Motor Disorders Project, Tokyo Metropolitan Institute of Medical Science / Laboratory for Behavioral Genetics, RIKEN Center for Brain Science / Department of Advanced Neuroimaging, IBIC, National Center of Neurology and Psychiatry, Japan

Information represented as internal models is stored in the brain in advance, so that we precisely control our movements without visual feedback information. There are two hypotheses of the internal models: forward model representing where to move and inverse model representing how to move. We demonstrate that a computational architecture employing a tandem configuration of forward and inverse models enables efficient motor learning by the plasticity on the synapses between parallel fibers and a Purkinje cell in the cerebellum. The theoretical model predicted adaptive motor learning observed in hand-reaching experiments in humans wearing a prism lens and explained the kinetic components of these behavioral adaptations. Patients with cerebellar degeneration disease showed behavioral impairments consistent with tandemly arranged internal models. Furthermore, their movements measured by motion capture system (Kinect v2) were unstable with the impairments of the cerebellar motor learning. It is possible to compare the cerebellar diseases with other neurological disorders (e.g. Parkinson's disease and dystonia) in the motion capture system. It might support to explore functions of other parts of the brain in the basis of the cerebellum.

Contribution of the Cerebellum to Predictive Motor Control and its Evaluation in Cerebellar Ataxia

Shinji Kakei[1]
Jongho Lee[2], Hiroshi Mitoma[3], Hirokazu Tanaka[4], Mario Manto[5,6], Christiane S. Hampe[7]

[1]Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan., [2]Komatsu University, Komatsu, Japan., [3]Medical Education Promotion Center, Tokyo Medical University, Tokyo, Japan., [4]Japan Advanced Institute of Science and Technology, Ishikawa, Japan., [5]CHU-Charleroi, Charleroi, Belgium., [6]Service des Neurosciences, University of Mons, 7000 Mons, Belgium., [7]University of Washington, School of Medicine, Seattle, WA 98109, USA

Goal-directed movements are predictive and multimodal in nature, especially for moving targets. For instance, during a reaching movement for a moving target, humans need to predict both motion of the target and movement of the limb. Recent computational studies show that the cerebellum predicts current and future states of the body and its environment using internal forward models. Sensory feedback signals from the periphery have delays in reaching the brain, ranging between tens to hundreds of milliseconds. It is well known in engineering that feedback control based on time-delayed inputs can result in oscillatory and often unstable movements. In contrast, the brain predicts a current state from a previous state using forward models. This predictive mechanism most likely underpins stable and dexterous control of reaching movements. Although the *cerebro-cerebellum* has long been suggested as loci of various forward models, few methods are available to evaluate accuracy of the forward models in patients with cerebellar ataxia. Recently, we developed a non-invasive method to analyze receipt of motor commands in terms of movement kinematics for the wrist joint (B_r/K_r ratio, Lee et al. 2015). In the present study, we have identified two components (F1 and F2) of the smooth pursuit movement. We found that the two components were in different control modes with different B_r/K_r ratios. The major F1 component in a lower frequency range encodes both velocity and position of the moving target (*higher* B_r/K_r ratio) to synchronize movement of the wrist joint with motion of the target in a *predictive* manner. The minor F2 component in a higher frequency range is biased to position control in order to generate intermittent small step-wise movements. In cerebellar patients, the F1 component shows a selective decrease in the B_r/K_r ratio, which is correlated with decrease in accuracy of the pursuit movement. We conclude that the B_r/K_r ratio of the F1 component provides a unique parameter to evaluate accuracy of the predictive control. We also discuss the pathophysiological and clinical implications for clinical ataxiology.

Targeting mutant ATXN2 to restore cerebellar function in the SCA2 mouse

Stefan Pulst

Department of Neurology, University of Utah, United States of America

Despite significant growth in the understanding of human neurodegeneration, the ability to modify the disease course in human neurodegenerative disease is still very limited. For those diseases, in which the underlying mendelian mutation is known, targeting the disease gene itself provides a unique opportunity to prevent disease initiation or to halt progression. We used two mouse models of spinocerebellar ataxia type 2 (SCA2) to test RNA-targeted therapies. SCA2 is an autosomal dominant disease caused by DNA CAG repeat expansion leading to a pathologically elongated polyglutamine tract in the ATXN2 protein. Both SCA2 mouse models recapitulate salient features of the human disease such as adult onset and progression of motor dysfunction and cerebellar Purkinje cell loss. Morphologic and behavioral changes are paralleled by progressive decline in the firing frequency of Purkinje cells as well as transcriptome and proteome changes. To develop a potential therapy directed at the ATXN2 gene we screened > 150 antisense oligonucleotides (ASOs). The most promising oligonucleotide, ASO7, downregulated ATXN2 mRNA and protein and resulted in slowed progression of the SCA2 phenotype. After delivery by intracerebroventricular injection to ATXN2-Q127 mice, ASO7 localized to Purkinje cells, reduced cerebellar ATXN2 expression below 75% for more than 10 weeks without microglial activation, and reduced the levels of cerebellar ATXN2. Treatment of symptomatic mice with ASO7 improved motor function compared to saline-treated mice. ASO7 had a similar effect in the BAC-Q72 SCA2 mouse model. In both mouse models ASO treatment normalized protein levels of several SCA2-related proteins expressed in Purkinje cells, including Rgs8, Pcp2, Pcp4, Homer3, Cep76 and Fam107b. Notably, the firing frequency of Purkinje cells returned to normal even when treatment was initiated more than 12 weeks after the onset of the motor phenotype in BAC-Q72 mice. These findings support ASOs directed against ATXN2 mRNAs as a promising approach for the treatment of human neurodegenerative diseases such as SCA2 and ALS in which ATXN2 plays a role in disease initiation or progression.

In vitro models of cerebellar development and spinocerebellar degeneration utilizing human iPSCs

Keiko Muguruma

Department iPS Cell Applied Medicine, Kansai Medical University / RIKEN (BDR), Japan

The ultimate goals of neuroscience are to understand human brain structures and functions, and to utilize them to overcome neurological disorders. The research on the human brain had long been limited to non-invasive MRI or PET studies, pathological analysis with postmortem brains or in-silico genomic analyses. Although animal or cellular models had been developed for investigating neurological disorders as alternatives to living human brain tissues, many of them did not represent correct human pathological phenotypes. In these circumstances, emergence of iPS cells and organoid culture systems provides us a novel way to investigate the development and dysfunction of the human brain tissues in vitro. We previously developed self-organizing 3D organoid culture of iPS cells for construction of human brain tissues. We succeeded in differentiation of mature cerebellar neurons including Purkinje cells with elaborated dendritic arbors. With this technique, we demonstrated that Purkinje cells derived from patients of various spinocerebellar ataxia exhibit vulnerabilities to the subtype-specific severe culture environment, and that these vulnerabilities were suppressed by treatment with specific compounds. The platform based on the techniques for iPS cell generation and self-organizing 3D culture will become a powerful tool for investigating human brain development and neurological diseases.

Mouse models of cerebellar ataxia using AAV-PHP.B, a capsid variant highly permeable to the blood brain barrier

Hirokazu Hirai

Gunma University Graduate School of Medicine, Japan

Spontaneous ataxic mice such as *staggerer* and *weaver* contributed significantly to unravel cerebellar functions. After cloning genes responsible for spinocerebellar ataxias (SCAs), transgenic mice overexpressing mutant genes were generated. A major drawback of those spontaneous and artificial mutants would be presence of developmental abnormalities. Patients of many neurodegenerative disorders grow normally, and start to show symptoms when the homeostasis is disrupted by aging-related accumulation of toxic molecules. Since mouse lifespan is around 2 years, high amount of mutant gene expression or expression of a degradation-resistant gene is required to cause neurodegeneration within the short lifespan. However, it is difficult to adjust the expression levels, and highly prone to cause developmental defects. To overcome this, we generated mouse models, using AAV-PHP.B highly permeable to the blood brain barrier. In this method, mature wild-type mice received intravenous injection of AAV-PHP.B that caused genetic and/or intracellular signaling defects recapitulating neurodegenerative diseases. We produced and analyzed different types of SCA model mice. Moreover, those model mice received a therapeutic intervention, which significantly mitigated aberrant phenotypes. Our results suggest a promise of AAV-based mouse models of neurodegenerative disorders for studying pathology and therapeutic interventions without contamination of irreversible developmental defects.

Developmental YAPdeltaC determines adult pathology of spinocerebellar ataxia type 1

Hitoshi Okazawa

Department of Neuropathology, Tokyo Medical and Dental University, Japan

YAP and its neuronal isoform YAPdeltaC are implicated in various cellular functions. We found that expression of YAPdeltaC during development, but not adulthood, rescued neurodegeneration phenotypes of mutant ataxin-1 knock-in (Atxn1-KI) mice. YAP/YAPdeltaC interacted with RORα via the second WW domain and served as co-activators of its transcriptional activity. YAP/YAPdeltaC formed a transcriptional complex with RORα on cis-elements of target genes and regulated their expression. Both normal and mutant Atxn1 interacted with YAP/YAPdeltaC, but only mutant Atxn1 depleted YAP/YAPdeltaC from the RORα complex to suppress transcription on short timescales. Over longer periods, mutant Atxn1 also decreased RORα *in vivo*. Genetic supplementation of YAPdeltaC restored the RORα and YAP/YAPdeltaC levels, recovered YAP/YAPdeltaC in the RORα complex and normalized target gene transcription in *Atxn1*-KI mice *in vivo*. Collectively, our data suggest that functional impairment of YAP/YAPdeltaC by mutant Atxn1 during development determines the adult pathology of SCA1 by suppressing RORα-mediated transcription.

Mesenchymal stem cells as a potential therapeutic candidate of multiple system atrophy-cerebellar type

Phil Hyu Lee

Department of Neurology, Yonsei University College of Medicine, Seoul, Korea /
Severance Biomedical Science Institute, Yonsei University, Seoul, Korea

Multiple system atrophy (MSA) is a rare, but the most catastrophic neurodegenerative disease with a prevalence of 4-20/100,000 people. MSA develops in relatively younger people (usually within the sixth decade) than other neurodegenerative diseases, progresses rapidly with a mean survival of 6 - 9 years after onset, and most patients have to be locked in a wheel-chair or a bed about half of their remaining lives. Tragically, no known agent is currently proved to ameliorate the deficits of MSA patients. Mesenchymal stem cells (MSC) are present in adult bone marrow and are capable of differentiating into various cell types. Additionally, MSC secrete various cytotrophic factors that, in turn, exert neuroprotective effects. Recently, animal studies demonstrated that human MSC had a protective effect against progressive dopaminergic and striatal neuronal loss in transgenic mice or double toxin-induced animals of MSA. Furthermore, we reported the results of an open-label trial and a randomized, double-blind, placebo-controlled trial of autologous MSCs in patients with MSA-cerebellar type, demonstrating that MSC treatment was associated with delayed progression of neurological deficits. Here, we will summarize recent progress in treatment of MSA, especially focusing on adult stem cells and discuss whether MSCs may act as one of new therapeutic alternatives in the future treatment of MSA-cerebellar type.

Molecular-targeted therapy for polyglutamine diseases.

Yoshitaka Nagai

Department of Neurotherapeutics, Osaka University Graduate School of Medicine, Japan

The polyglutamine (polyQ) diseases, including various spinocerebellar ataxias (SCA1, 2, 3, 6, 7, 17, DRPLA), Huntington's disease, and spinal and bulbar muscular atrophy (SBMA), are caused by an abnormal expansion of the polyQ stretch (>35-40) in the disease-causative proteins, which triggers their misfolding, aggregation, and accumulation as inclusion bodies, eventually leading to neurodegeneration. Toward developing a molecular-targeted therapy for the polyQ diseases, we screened small chemical compound libraries for polyQ aggregation inhibitors using our *in vitro* polyQ aggregation assay. Among the polyQ aggregation inhibitors we identified, we focused on QAI1 (PolyQ Aggregation Inhibitor 1), which is a clinically-approved drug and is known to cross the blood-brain-barrier, as a therapeutic candidate. We demonstrated that QAI1 inhibits the β-sheet conformational transition of the expanded polyQ protein *in vitro*. We further showed that QAI1 suppresses the polyQ-induced eye degeneration in a *Drosophila* model of SCA3. Furthermore, we successfully demonstrated that oral administration of QAI1 ameliorates the motor impairment and reduces polyQ inclusions in mouse models of SCA1 and SBMA. Most importantly, administration of QAI1 to SCA1 mice from after the symptom onset could also ameliorate their motor impairment. These results demonstrate the potential of QAI1 as a therapeutic molecule for the polyQ diseases.

Introduction to a clinical trial with mesenchymal stem cell transplantation for SCA

Bing-Wen Soong

Department of Neurology, Taipei Medical University-Shuang-Ho Hospital, Taipei, Taiwan

Ataxia is one of the most devastating symptoms of many neurodegenerative disorders. As of today, there isn't any effective treatment to retard its progression. Mesenchymal stem cells (MSCs) have shown promise in treating neurodegenerative diseases. We conducted a phase I/IIa clinical study in Taiwan several years ago to primarily evaluate the safety, tolerability and, secondarily, the possible efficacy of intravenous administration of allogeneic adipose tissue-derived MSCs from healthy donors. No adverse events related to the injection of MSCs during the one year follow-up were observed. The intravenous administration of allogeneic MSCs seemed well tolerated. Both outcome measures showed early improvement in neural function. We concluded that the results were supportive of advancement of the allogeneic MSCs treatment in a randomized, double-blind, placebo-controlled phase 2 trial. A course of multiple MSC IV infusions may enhance or prolong the functional improvement observed in the Phase I/II study.

— Poster Presentation —

P-1 Roles of synaptic activity in climbing fiber to Purkinje cell synapse elimination in the developing cerebellum

Tzu-Huei Kao

International Research Center for Neurointelligence (WPI-IRCN), UTIAS, The University of Tokyo

In the nervous system of neonatal animals, synaptic connections are initially weak and excessive, but necessary connections are selectively strengthened while unnecessary ones are eliminated during postnatal development through a series of events termed synapse elimination. Experimental evidence suggests that axons conveying stronger synaptic inputs than the others are selectively strengthened and their synaptic connections to target cells are stabilized, while connections from the other axons are destabilized and eventually removed, presumably through competitions for limited resource and space on postsynaptic cells. However, it remains unclear whether the ultimate "winner" axons are selected purely by the difference in the strength of synaptic inputs. In the present study, we aimed to tackle this issue using climbing fiber (CF)-Purkinje cell (PC) synapses in the developing cerebellum. In the neonatal mice, PCs are innervated by multiple CFs with similar strengths. Then, a single "winner" CF is selectively strengthened and subsequently translocated to PC dendrites whereas the other "loser" CFs are eliminated. To examine to what extent synaptic inputs influence CF synapse elimination, we created an experimental model where "absolutely weaker CFs" with deprived glutamate release compete their intact opponents in neonatal mice. We will present results of our on-going research on this model.

P-2 Phospholipase C β3 mediates climbing fiber synapse elimination in aldolase C-positive compartments of the developing mouse cerebellum

Takaki Watanabe[1,2], Yurie Rai[1], Masanobu Kano[1,2]

[1]Department of Neurophysiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]International Research Center for Neurointelligence (WPI-IRCN), The University of Tokyo Institutes for Advanced Study (UTIAS), The University of Tokyo

Functionally-matured neural circuits are shaped by elimination of early-formed redundant synapses during postnatal development. In the cerebellum of neonatal mice, multiple climbing fibers (CFs) form synapses on each Purkinje cell (PC). One CF is strengthened in each PC from P3 to P7, and then the other weaker CFs are eliminated from P8 to P17. Type 1 metabotropic glutamate receptor (mGluR1) triggers the late phase of CF elimination from P12 to P17. Among downstream signaling molecules of mGluR1, phospholipase C β4 (PLCβ4) and β3 (PLCβ3) are expressed complementarily in PCs of aldolase C (Aldoc)-negative and -positive compartments, respectively. We previously demonstrated that PLCβ4 is required for the late phase of CF elimination in the rostral vermis. However, it remains unclear which PLCβ subtype(s) mediate(s) CF synapse elimination in the caudal vermis where PCs express Aldoc. To address this question, we used heterozygous Aldoc-tdTomato knock-in mice and knocked down PLCβ3 in PCs by injecting lentivirus carrying miRNA against PLCβ3. Our electrophysiological examination revealed that in Aldoc-positive compartments, significantly higher percentage of PCs with PLCβ3-knockdown remained innervated by multiple CFs than control PCs after P12. We thus conclude that PLCβ3 is required for the late phase of CF synapse elimination in Aldoc-positive PCs.

P-3 Organization of internal copy neural circuits for skilled forelimb movement

Hermina Nedelescu, James Conner, Nick Baltar, Phong Nguyen, Eiman Azim

Molecular Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, CA

One picks up a glass of water differently each time, but rarely spills it. This consistency in execution suggests that feedback information is used to continuously adjust motor output and ensure task-specific refinement. One rapid form of feedback enabling swift correction may be provided by neural pathways that convey copies of ongoing forelimb motor commands to cerebellar circuits. The lateral reticular nucleus (LRN) in the caudal brainstem serves as a major relay of internal copy information, given its innervation by spinal copy pathways, and output to the cerebellum. However, the organization of the LRN and how it contributes to movement remain poorly defined; we have little understanding of LRN neuronal subtypes, how LRN neurons are anatomically organized in relation to incoming spinal copy pathways and outgoing cerebellar targets, and how LRN neural circuits contribute to the regulation of forelimb motor output. Taking advantage of mouse genetics and molecular tools, we identified novel neuronal subtypes in the LRN, mapped the innervation patterns of multiple LRN-projecting spinal afferent pathways, and identified brain-wide inputs to distinct LRN-projecting cervical propriospinal neurons. These results provide a deeper understanding of forelimb internal copy circuit organization and how the LRN might convey these signals to the cerebellum.

Funding sources: NINDS R00NS088193, Searle Scholars Program, Pew Scholars Program, Salk Women in Science Award

---

P-4 Morphology of single pontocerebellar axons in relation to zebrin stripes and lobules in the mouse cerebellum.

Mohammad Shahangir Biswas, Yuanjun Luo, Izumi Sugihara

Tokyo Medical and Dental University, Department of Systems Neurophysiology

To understand mechanisms cerebrocerebellar link, it is important to know the anatomical organization of the pontocerebellar mossy fiber projection, details of which have not been much clarified. We reconstructed pontocerebellar axons labeled with anterograde tracer biotinylated dextran amine (BDA) injected into various positions of the pontine nucleus (PN) in the mouse. Terminals were mapped by referring to immunostained zebrin (aldolae C) stripes in the cerebellar cortex. So far we reconstructed 25 pontocerebellar axons completely in 9 mice. The majority, but not all, of axons enter the cerebellum through the middle cerebellar peduncle contralateral to the soma. A small number of axons (3 out of 25) had collaterals terminating in the cerebellar nuclei. Axons projected to a combination of lobules often bilaterally and terminated more frequently in zebrin-positive stripes than in zebrin-negative stripes, with 65 mossy fiber terminals on the average. Axons originating from the rostromedial PN mainly terminated in the paraflocculus, crus I and lobule VI, while axons originating from the central PN mainly terminated in the simplex lobule, crus II and paramedian lobule. The results suggest affinity among particular combination of cerebellar lobules, according which the pontocerebellar projection is organized topographically.

P-5 Possible involvement of cerebellum in expertise in a cognitive domain

Hironori Nakatani

The University of Tokyo

The cerebellum is well known to contribute to skilled motor control. During a motor learning, the cerebellum encodes an internal model that is a neural representation of dynamics in body parts. The internal model in the cerebellum makes it possible to control learned movements quickly and precisely without any reference to feedback of sensory information. Masao Ito have proposed that the cerebellum also encodes an internal model that represents the essential properties of mental representations in the cerebral cortex and this internal model contributes to intuition and implicit thought. As intuition and implicit thought are prominent properties of expertise in cognitive domain, I hypothesize that the cerebellum contributes to expert performances in cognitive domain by encoding an internal model of cognitive functions. I have tested this possibility with a board game named shogi (Japanese chess). Expert shogi players solved shogi problems in a scanner of magnetic resonances imaging. When participants solved the problems intuitively and quickly, the lateral parts of the cerebellum showed larger activations. The result supports Masao Ito's proposal that the internal model of the cerebellum controls mental activities.

P-6 Functional compartmentalization of the cerebellar circuits: three-dimensional analysis in zebrafish

Kanae Hiyoshi[1], Kanoko Okumura[1], Hiroaki Miyazawa[1], Narumi Fukuda[2], Hitoshi Okamoto[3], Kyo Yamasu[1], Sachiko Tsuda[1,4]

[1]Graduate School of Science and Engineering, Saitama University, [2]Faculty of Science, Saitama University, [3]RIKEN Center for Brain Science, [4]Research and Development Bureau, Saitama University

The general anatomical organization of the cerebellar neural circuits is well defined; however, its functional organization and development are still unresolved. To address this issue, especially focusing on cerebellar compartmentalization, we have applied optical approaches and behavior analysis to zebrafish, an ideal model system for studying neurogenesis and optical techniques.

To examine functional activity in the cerebellum, we conducted high-speed calcium imaging of neural activity which was combined with optokinetic response (OKR) test. Three-dimensional analysis using the obtained data revealed that four groups of Purkinje cells showed distinct patterns of activity, and were distributed differently along dorso-ventral axis, forming clusters in a 3D manner. Optogenetic stimulation targeting the activated regions repressed OKR, suggesting that they were important for the eye movement. These findings suggest the 3D structure and roles of functional compartments in the developing cerebellum.

Furthermore, we have also applied recently developed genetically encoded voltage indicators, ASAP1 (Accelerated Sensor of Action Potentials 1) to zebrafish larvae, and succeeded in detecting the evoked activity in the cerebellum as well as the spontaneous activity in the spinal cord neurons at the single cell level. We have also succeeded in the visualizing the inhibition in the zebrafish cerebellum by voltage imaging.

P-7 Sensory prediction signals in the primate cerebellar nuclei during synchronized saccades

Ryuji Takeya, Masaki Tanaka

Department of Physiology, Hokkaido University

Temporal prediction is essential for synchronized movements. To examine the role for the cerebellum, neuronal activities were recorded from the dentate nucleus in a behaving monkey. In the synchronized saccade task (Takeya et al., *Sci Rep*, 2017), the animal generated sequential saccades to alternately presented visual stimuli. In the predictive condition, the target was alternated at a fixed interval (400, 550 or 700 ms, selected randomly for each trial), and synchronized saccades with target onset (within ± 20% of interval) were reinforced by liquid reward. In the control condition, the target interval was randomized within each trial, and reactive saccades following the target onset (> 150 ms) were reinforced. So far, we have recorded from 36 saccade-related neurons. Among them, one third of neurons exhibited greater firing modulation for the predictive than control conditions. Approximately 44% neurons responded to saccades in both directions. Remarkably, a subset of these bidirectional neurons showed predictive activity for target onset even during the initial few cycles, when the animal generated reactive saccades. The timing of predictive activity altered in a block consisting of longer intervals (700 and 1000 ms). These results suggest that the cerebellum may generate sensory prediction signals required for synchronized movements.

P-8 Comparison of electrophysiological characteristics of zebrin-positive and -negative Punkinje cells

Viet T Nguyen-Minh, Anh Tran, Yuanjun Luo, Izumi Sugihara

Tokyo Medical and Dental University, Department of Systems Neurophysiology

Subsets of cerebellar Purkinje cells (PCs) that have a particular molecular expression profile are arranged into separate longitudinal stripes, which have different topographic afferent and efferent axonal connections to be involved in different functions. Expression levels of many molecules such as glycolysis enzyme aldolase C (zebrin) and glutamate transporter EAAT4 are linked together among PC subsets, suggesting different physiological properties among them. We recorded from zebrin-positive (Z+) and -negative (Z-) PCs in vermal lobule VIII in cerebellar slice preparations from Aldoc-Venus mice. No significant differences were observed in input resistance or in occurrence probability of types of firing patterns between Z+ and Z- PCs. Also, no significant differences were observed either between Z+ and Z- PCs in interval dependency of paired pulse facilitation or in time course of synaptic current in parallel fiber (PF)-PC synapse. These results indicate that molecular expression differences associated with the zebrin type do not directly affect basic electrophysiological properties of PCs or PF-PC synapse. The results suggest that differences in climbing fiber (CF) activity and in CF-PC synaptic property, as well as some region (lobule)-dependent differences in PC properties, may be involved in heterogeneous electrophysiological properties in PC subsets reported in *in vivo* preparation.

P-9 Cerebellar integration of multiple input signals

Misa Shimuta[1], Izumi Sugihara[2], Taro Ishikawa[1]

[1]Department Pharmacology, Jikei University School of Medicine, Tokyo, Japan, [2]Department Systems Neurophysiology,Tokyo Medical and Dental University, Tokyo, Japan

Somatosensory signals from the facial area are conveyed to the cerebellar granule cells via direct trigeminocerebellar (TC) and indirect cortico-ponto-cerebellar (CPC) pathways, while Purkinje cells receive climbing fiber signals. To reveal how these multiple types of signals are integrated in the cerebellar cortical circuit, we made whole-cell recordings from granule cells and unit recording from Purkinje cells in transgenic (VGAT-ChR2) mice, whose CPC pathway could be optogenetically blocked to the somatosensory cortex (SI). When tactile stimulation was given to the upper lip, excitatory synaptic currents in the granule cells appeared in two distinct timings. The early response (~10 ms latency) was not affected but the late response (~30 ms latency) was suppressed by the block in SI, suggesting that they were responses via TC and CPC pathways, respectively. Similarly, in Purkinje cells, the early simple spikes were not affected, but the late simple spikes and the complex spikes are suppressed by SI block. Furthermore, by using knock-in mice in which aldolase C bands were visualized by fluorescent protein, we found that each band in crus II had different proportion of TC and CPC responses. These results demonstrate the manner in which the cerebellar cortex integrates signals via multiple pathways.

P-10 Sensory contributions to encoding of whisker movement in lateral cerebellum

Paul Chadderton[2], Tunvez Boulic[1], Claudia Clopath[1]

[1]Centre for Neurotechnology and Department of Bioengineering, Imperial College London, UK, [2]School of Physiology, Pharmacology and Neuroscience, University of Bristol, UK

Tactile sensing is used by animals to examine their immediate environments. The precise movements generated to gain feedback are the result of active processes whereby motor commands and sensory consequences are integrated. The cerebellum is involved in sensorimotor integration and cerebellar activity is modulated during whisking in rodents. During voluntary movement in the absence of touch, cerebellar neurons linearly encode whisker position via changes of simple spike (SS) firing rate [1]. Although evidence indicates that this signal could be attributed to a motor command [2], the cerebellum is also known to receive sensory feedback opening the likelihood of their integration.

To address this issue, we investigated the encoding of sensory input generated by exogenous movements of whiskers in cerebellar Purkinje cells (PCs). We observed robust sensory-evoked responses to single whisker deflections in 11 out of 13 PCs. The exclusively negative modulation induced a maximal decrease of 16.3 ± 6% in SS firing rate. Interestingly, the duration of the modulation was extended with respect to whisker movement, in contrast to temporally faithful encoding of position in the absence of touch. These results suggest that sensorimotor interaction at the level of cerebellar PCS is likely to contribute towards active sensing.

[1] Chen, S., Augustine, G. J., & Chadderton, P. (2016). The cerebellum linearly encodes whisker position during voluntary movement. ELife, 5, e10509. https://doi.org/10.7554/eLife.10509

[2] Brown, S. T., & Raman, I. M. (2018). Sensorimotor Integration and Amplification of Reflexive Whisking by Well-Timed Spiking in the Cerebellar Corticonuclear Circuit. *Neuron*, *99*(3), 564-575.e2. https://doi.org/10.1016/J.NEURON.2018.06.028

P-11 Thalamocortical axonal activity in motor cortex exhibits layer-specific dynamics during motor learning

Yasuyo H. Tanaka[1], Yasuhiro R. Tanaka[1], Masashi Kondo[1], Shin-Ichiro Terada[1], Yasuo Kawaguchi[2], Masanori Matsuzaki[1]

[1]Department of Physiology Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Division of Cerebral Circuitry, National Institute for Physiological Sciences, Okazaki, Japan

Through motor learning, animals acquire the skilled movements needed to efficiently accomplish their goals in everyday life. In motor circuits, subcortical and cortical structures are interconnected in real time, with the primary motor cortex sending motor outputs to the spinal cord. The thalamus is the hub through which neural signals are transmitted from the basal ganglia and cerebellum to the neocortex. However, thalamocortical axonal activity during motor learning remains largely undescribed. We conducted two-photon calcium imaging of thalamocortical axonal activity in the motor cortex of mice learning a self-initiated lever-pull task. Layer 1 (L1) axons came to exhibit activity at lever-pull initiation and termination, while layer 3 (L3) axons did so at lever-pull initiation. L1 population activity had a sequence structure related to both lever-pull duration and reproducibility. Stimulation of the substantia nigra pars reticulata activated more L1 than L3 axons, whereas deep cerebellar nuclei (DCN) stimulation did the opposite. Lesions to either the dorsal striatum or the DCN impaired motor learning and disrupted temporal dynamics in both layers. Thus, layer-specific thalamocortical signals evolve with the progression of learning, which requires both the basal ganglia and cerebellar activities.

P-12 Increase of end-point errors in reaching induced by microstimulation to the red nucleus

Masato Inoue[1], Shigeru Kitazawa[1,2,3,4]

[1]Endowed Research Department of Clinical Neuroengineering, Global Center for Medical Engineering and Informatics, Osaka University, Suita, Osaka, Japan, [2]Dynamic Brain Network Laboratory, Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka, Japan, [3]Department of Brain Physiology, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan, [4]Center for Information and Neural Networks (CiNet), National Institute of Information and Communications Technology, and Osaka University, Japan

We have recently shown that neurons in the motor and parietal cortices encode information on end-point errors in reaching, and that post-movement microstimulation to these regions causes trial-by-trial increases in errors. Based on these results we suggested that these areas provide error signals that drive trial-by-trial adaptation in reaching movement. The red nucleus (RN) receives inputs from motor and parietal cortices and sends output to the climbing fibers of the cerebellar cortex via the inferior olivary nucleus. To test whether the error signals in RN are causally related to adaptation in reaching, we examined neuronal activities of RN while two monkeys made rapid reaching movements toward a visual target. Approximately half of the RN neurons encoded information on target positions before the onset of movement and/or visual errors after the end of movement. These results were similar to those of complex spikes of Purkinje cells. We then delivered electrical microstimulation after the touch by using the same electrode. Repetitive pairing of reaching movements with microstimulation produced a gradual and significant increase of the endpoint error opposite to the preferred direction of visual errors. These results suggest that the RN provide error signals that drive trial-by-trial adaptation in reaching movement.

P-13 Acquisition and maintenance of predictive optokinetic response depend on the cerebellum

Shuntaro Miki[1], Robert Baker[2], Yutaka Hirata[1,3]

[1]Computer Science, Chubu University Graduate School of Engineering, Aichi, Japan, [2]Physiology and Neuroscience, New York University School of Medicine, New York, USA, [3]Robotic Science and Technology, Chubu University College of Engineering, Aichi, Japan

Optokinetic reflex (OKR) tracking is induced by the presentation of large field visual motion in nearly all vertebrate species. If the same periodic visual stimulus is given continuously, the OKR gain (eye velocity / visual motion velocity) increases up to 1.0. In addition to gain increase, goldfish acquires predictive OKR that was named period tuning. Namely, after continuous exposure to a periodic visual motion, goldfish OKR velocity decreases as if it predicts the timing of the change in visual motion direction (Marsh & Baker, 1997). Here we examined roles of the cerebellum in this predictive OKR by employing cerebellectomy before and after acquisition of the predictive OKR. We demonstrate that the cerebellum appears necessary for both acquisition and maintenance of the predictive OKR.

P-14 Regulation of motor learning and synaptic plasticity by β-adrenergic receptor in the cerebellar flocculus

Takuma Inoshita, Tomoo Hirano

Department of Biophysics, Graduate School of Science, Kyoto University

The cerebellum contributes to motor learning, and adaptations of reflex eye movements, the vestibulo-ocular reflex (VOR) and optokinetic response (OKR), have been studied as models of cerebellum-dependent motor learning. Previous studies reported involvement of cerebellar adrenergic systems in regulation of oculomotor reflex. We have reported contribution of β-adrenergic receptors in the cerebellar flocculus to OKR control and adaptation. Application of β-adrenergic agonist increased the OKR gain and that of antagonist suppressed the gain increase in adaptation of OKR. These results suggest that activation of β-adrenergic receptor is involved in OKR adaptation. On the other hand, it has also been reported that synaptic plasticity at parallel fiber to Purkinje neuron (PF-PN) synapse in the cerebellum plays an important role in motor learning. Recently, we demonstrated that long-term depression (LTD) occurred at PF-PN synapses in the flocculus during adaptation of OKR. Taken together, we considered that norepinephrine modulated synaptic plasticity at PF-PN synapses in the cerebellar flocculus. Here, we report that LTD was facilitated by application of β-adrenergic agonist at PF-PN synapses in the flocculus, suggesting that β-adrenergic receptors regulate motor learning by modulating synaptic plasticity at PF-PN synapses in the cerebellar flocculus.

P-15 Large-scale simulations of the cerebellum and cortico-thalamo-cerebellar circuit on K supercomputer

Hiroshi Yamaura[1], Jun Igarashi[2], Tadashi Yamazaki[1]

[1]The University of Electro-Communications, [2]RIKEN Head Office for Information Systems and Cybersecurity

To understand the function of the brain, simulation of a realistic neural network model is a useful method. In addition, it is considered that human-scale whole-brain simulations become possible using an exaflops supercomputer.

We developed a spiking neural network model of the cerebellum based on electrophysiological and anatomical data using neural network simulator. The simulator performs the tile partitioning method. We investigated weak scaling performance using 1024~40000 computational nodes of Japanese K supercomputer. The result showed that computational time did not increase with the increase in the size of the network, which means the parallelization method achieved good scaling performance. Using 40000 nodes, our cerebellar model is composed of 32 billion neurons. The results suggest that we can build a human-scale cerebellar model on exaflops supercomputer.

The cerebellum and the cerebral cortex form the cerebro-cerebellar communication loop. The loop seems to play an important role in learning and cognitive functions. In addition to the cerebellar model, we developed spiking neural network model of the primary motor cortex and the thalamus. We built cortico-thalamo-cerebellar circuit on K supercomputer. Here we report the results of performing the simulation.

These results may become a fundamental step toward human-scale whole-brain simulations.

P-16 iPatax: tablet computer (iPad®) application software for evaluating cerebellar ataxia

Takahiro Nagai[1], Masayoshi Tada[2], Osamu Onodera[1]

[1]Department of Neurology, Brain Research Institute, Niigata University, [2]Department of Neurology, Niigata City General Hospital

Scale for the Assessment and Rating of Ataxia (SARA) is widely used as the primary endpoint in clinical trials for cerebellar ataxias; however, the categorical scale using discrete variables lacks sensitivity and accuracy needed to detect the small changes in motor coordination of patients with spinocerebellar degeneration (SCD). In addition, the inter- and intra-rater variability might be problem in multi-institutional clinical trials. To develop a more sensitive and reliable evaluation method for quantitative assessment of cerebellar ataxia, we developed an iPad application software, the iPatax (iPad® application software for evaluating ataxia). The software includes Visually-Guided Tracking Movement Test (VGTMT), in which subjects were required to maintain the position of their second finger within a target moving at a constant speed. We analyzed the correlation between SARA scores and data obtained from iPatax. We found that the coefficient of variation (CV) of velocity of the finger in VGTMT highly correlated with SARA total scores. Moreover, the rate of improvement in tracking movements of patients with SCD was negatively correlated with SARA total scores, suggesting that motor learning was impaired in the patients with SCD. We have proposed a promising method, iPatax, for evaluating ataxias that can be performed anytime and anywhere.

P-17 Cerebellar degeneration reduces memory resilience after extended training

Opher Donchin, T. Hulst, D. Timann

Department of Biomedical Engineering and Zlotowski Center for NeuroscienceBen-Gurion University of the Negev

We explored the possibility that different training regimes can lead to better long term retention by testing them in control subjects age matched to subjects with cerebellar ataxia. Using a reaching movement adaptation paradigm, we tested three different regimes that had been proposed in the literature as candidates for producing memories that have more "slow learning" and less "fast learning." Slow learning is also associated with slower forgetting and greater long term retention. We tested for increased slow learning by testing the resilience of the memories to a counter-adaptation. We found that only one regime -- extended training for many trials -- increased the slow learning. However, this effect was much larger for control subjects than for patients with cerebellar ataxia. Our findings highlight both the importance of understanding how training regimes can influence learning and retention and the importance of testing how well a specific training regime can transfer to a specific population with cerebellar related disorders.

P-18 Pharmacological enhancement of retinoid-related orphan receptor α function mitigates spinocerebellar ataxia type 3 pathology

Masashi Watanave, Chiaki Hoshino, Ayumu Konno, Yumi Fukuzaki, Yasunori Matsuzaki, Tohru Ishitani, Hirokazu Hirai

Department of Neurophysiology and Neural Repair, Gunma University Graduate School of Medicine

Cerebellar Purkinje cells (PCs) are the sole output neurons of the cerebellar cortex, and damage to PCs results in motor deficits. Spinocerebellar ataxia type 3 (SCA3), a hereditary neurodegenerative disease, is caused by an abnormal expansion of the polyglutamine tract in the causative ATXN3 protein. SCA3 affects a wide range of cells in the central nervous system, including those in the cerebellum. To unravel SCA3 pathology, we used adeno-associated virus serotype 9 (AAV9) vectors to express full-length ATXN3 with an abnormally expanded 89 polyglutamine stretch (ATXN3[Q89]) in cerebellar neurons of mature wild-type mice. Mice expressing ATXN3[Q89] exhibited motor impairment. Immunohistochemistry of the cerebellum showed ubiquitinated nuclear aggregates in PCs; degeneration of PC dendrites; and a significant decrease in multiple proteins including retinoid-related orphan receptor α (RORα), a transcription factor, and type 1 metabotropic glutamate receptor (mGluR1) signaling molecules. Patch-clamp analysis of ATXN3[Q89]-expressing PCs revealed marked defects in mGluR1 signaling. Notably, the emergence of behavioral, morphological, and functional defects was inhibited by a single injection of SR1078, an RORα/γ agonist. These results suggest that RORα plays a key role in mutant ATXN3-mediated aberrant phenotypes and that the pharmacological enhancement of RORα could function as a method for therapeutic intervention in SCA3.

P-19 Calcium channel antibody as a possible etiology of treatable cerebellar ataxias: A case report.

Takashi Irioka[1], Masakatsu Motomura[2], Kinya Ishikawa[3], Toshiki Uchihara[4], Takanori Yokota[5]

[1]Department of Neurology, Yokosuka Kyosai Hospital, Kanagawa, Japan, [2]Department of Electrical and Electronics Engineering, Faculty of Engineering, Nagasaki Institute of Applied Science, Nagasaki, Japan, [3]The Center for Personalized Medicine for Healthy Aging, Tokyo Medical and Dental University, Tokyo, Japan, [4]Neurology Clinic with Neuromorphomics Laboratory, Nitobe Memorial Nakano General Hospital, Tokyo, Japan, [5]Department of Neurology and Neurological Sciences, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

Objectives: Paraneoplastic cerebellar degeneration (PCD) is an autoimmune-mediated disorder and usually associated with onconeural antibodies (e.g., anti-Yo abs). PCD is generally treatment resistant, and complete loss of Purkinje cells is a pathological hallmark. P/Q-type voltage-gated calcium channel antibodies (P/Q-VGCC abs) are pathogenic for Lambert-Eaton myasthenic syndrome (LEMS), but they can also be associated with PCD. It remains unclear whether P/Q-VGCC abs are pathogenic for PCD. Methods: We present clinical features of a patient with small cell lung cancer (SCLC)- and P/Q-VGCC-ab-associated PCD without LEMS. Results: A 69-year-old man developed subacute pancerebellar syndrome. Systemic investigations revealed SCLC. Brain MRI was unremarkable, but lymphocytosis was present in the cerebrospinal fluid. He showed immediate response to both oncologic and immunologic therapies. In particular, it took just 16 hours for his response to plasma exchange (PLEX)! The patient was treated with radiotherapy against brain metastases, but he died of metastasis to the cauda equina 3.5 years after onset. The patient was autopsied, and pathological examination is now in progress. Discussion: Immediate response to antibody-depleting therapy such as PLEX could suggest a functional pathogenic effect of P/Q-VGCC abs on PCD. Ongoing pathological study might reveal differences between onconeural ab- and P/Q-VGCC-ab-associated PCDs.