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REVIEW

Redefining cerebellar ataxia in degenerative ataxias: lessons from recent research on cerebellar systems

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ABSTRACT

Recent advances in our understanding of neurophysiological functions in the cerebellar system have revealed that each region involved in degenerative ataxias contributes differently. To regulate voluntary movements, the cerebellum forms internal models within its neural circuits that mimic the behaviour of the sensorimotor system and objects in the external environment. The cerebellum forms two different internal models: forward and inverse. The forward model is formed by efference copy signals conveyed by the corticopontocerebellar system, and it derives the estimated consequences for action. The inverse model describes sequences of motor commands to accomplish an aim. During motor learning, we improve internal models by comparing the estimated consequence of an action from the forward model with the actual consequence of the action produced by the inverse model. The functions of the cerebellum encompass the formation, storage and selection of internal models. Considering the neurophysiological properties of the cerebellar system, we have classified degenerative ataxias into four types depending on which system is involved: Purkinje cells, the corticopontocerebellar system, the spinocerebellar system and the cerebellar deep nuclei. With regard to their respective contributions to the internal models, we speculate that loss of Purkinje cells leads to malformation of the internal models, whereas disturbance of the afferent system, corticopontocerebellar system or spinocerebellar system leads to mis-selection of the proper internal model. An understanding of the pathophysiological properties of ataxias in each degenerative ataxia enables the development of new methods to evaluate ataxias.

INTRODUCTION

Ataxia, originally derived from the Greek word meaning 'lack of order', signifies a disturbance of voluntary motor coordination. In 1899, Babinski proposed the concept of 'asynergy', a disturbance of coordination of the muscles involved in specific voluntary movements.[1] He also used the terms 'decomposition' and 'adiadochokinesis' to delineate the signs and symptoms of asynergia, as well as 'hypermetria' in movement extending a limb to the target. Holmes highlighted another important feature of ataxia: 'delayed initiation' of voluntary movements. 'Dyschronometria' is a temporal variability in the contraction of individual muscles, including agonists as well as antagonists, which is characteristic of cerebellar symptoms, including asynergia, decomposition and adiadochokinesis.[1] These clinical symptoms have been observed in repeated, discontinuous and visually guided reaching movements. However, the underlying neurophysiology of these symptoms has not been fully explained, and the anatomical regions responsible for these symptoms remain unknown. It is necessary to reconsider ataxias in terms of the physiological functions of the cerebellar system and the neuropathology associated with each type of degenerative ataxia. To address these issues, understanding how the cerebellum regulates our actions is essential.

ATAXIA IN THE CONTEXT OF CEREBELLAR FUNCTION

The cerebellum has multiple functions in the context of motor regulation, learning and behaviour.[1 2] Regarding motor regulation, the cerebellum has been proposed to form 'internal models' that mimic the behaviour of the sensorimotor system and objects in the external environment.[3–6] The internal models enable us to predict the consequences of motor commands and to select the best sequence of motor commands for accomplishing a specific aim.[3–6] The cerebellum forms two different types of internal model: forward and inverse.[7] The forward model is formed by the efference copy signals conveyed by the corticopontocerebellar system, and it derives the estimated consequences of an action.[2–4 7–11] The inverse model provides the best motor command estimated for the desired consequence, and orchestrates individual muscles, including agonists and antagonists, during an action.[3 4 7–13] The information about estimated consequences of the action is necessary to assess the actual consequences.[10] By comparing information about estimated consequences from the forward model with the actual consequences from the inverse model, the internal model can be improved to increase the accuracy and smoothness of the action the next time it is performed.[10–13] The forward and inverse model are suggested to be tightly coupled, with multiple paired forward and inverse models existing in the cerebellum.[3 7] The forward model selection automatically determines the coupled inverse model, from which information is conveyed to the motor cortex by the dentate-thalamic pathway, resulting in an action.[14] This process of formation, storage and selection of internal models is one of the main functions of the cerebellum.[1 4–6 10–13] We speculate that degenerative ataxias may differ from each other in terms of internal model relationships. To discuss this possibility, we first review the function of each part of the cerebellar system.

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THE CEREBELLAR CORTICAL CIRCUIT: INTERNAL MODEL FORMATION

The structure of neuronal circuits is relatively identical in all areas of the cerebellar cortex.[9 15] Two types of neurons, granule and Purkinje cells and at least four types of interneurons compose the network in the cerebellar cortex. These neurons are arranged as repeating units in a highly regular manner, each of which is a basic circuit module. The granule cells receive excitatory signals from mossy fibres arising from neurons in the brainstem or spinal cord, mainly via the middle or inferior cerebellar peduncle. The information from 25 million mossy fibres is dispersed to ~50 billion granule cells.[15] Then the information of the granule cells is conveyed to 15 million Purkinje cells via excitatory signals from parallel fibres arising from the granule cells (figure 1).[15] Each Purkinje cell also receives excitatory signals from a single climbing fibre arising from the inferior olive neurons in the medulla; each climbing fibre contacts 1–10 Purkinje cells.[2] A group of several hundred or thousand Purkinje cells composes a microzone, which is an effective cerebellar functional unit.[2] The Purkinje cells within the same microzone transmit inhibitory signals to the same small cluster of cells within the deep cerebellar nuclei.[2] The initial trace for the memory of a motor sequence is speculated to be stored in the cerebellar cortical circuit; this memory may be consolidated in the cerebellar deep nuclei.[16] This extensive transmission of information from mossy fibres to granule cells and into Purkinje cells is believed to provide a computational benefit for the cerebellar system.[15] The number of microzones might define the quantity of the internal model, while disorder in the cerebellar circuit may affect the quality of the internal model. Therefore, the loss of Purkinje cells may initially affect the quality of the internal model, but not the quantity (figure 2B).[15] A massive depletion of Purkinje cells might eventually decrease the number of microzones, resulting in a quantifiable depletion in the internal model.[2 3 9 10 13 17]

MOSSY FIBRES: THE AFFERENT PATHWAY FROM THE CEREBRUM AND BODY PERIPHERY

Mossy fibres are the most numerous afferent fibres terminating in the granular layer, where they form moss-like structures. Most mossy fibres arise from neurons located within the brainstem and spinal cord. Mossy fibres convey information from the cerebral cortex, brainstem and spinal cord to the cerebellum (figure 1).[9 15] The corticopontocerebellar system is associated with skilled movements or fine motor movements, such as those involved in writing, speaking or playing an instrument,[10 18 19] whereas the spinocerebellar or vestibulocerebellar systems are associated with actions that require continuous feedback information, such as those involving standing or gait.[12 15 20–22]

The cerebellum receives instruction about an intended action from a higher centre in the cerebrum such as the supplementary motor cortex or premotor cortex via the corticopontocerebellar system (efference copy signal).[8 10] The pontine nuclei, located in the pontine base, relay this information from the higher centre to the contralateral cerebellar cortex of the lateral parts of the hemisphere (cerebrocerebellum) through the middle cerebellar peduncle via mossy fibres.[21] With this information, the cerebellar

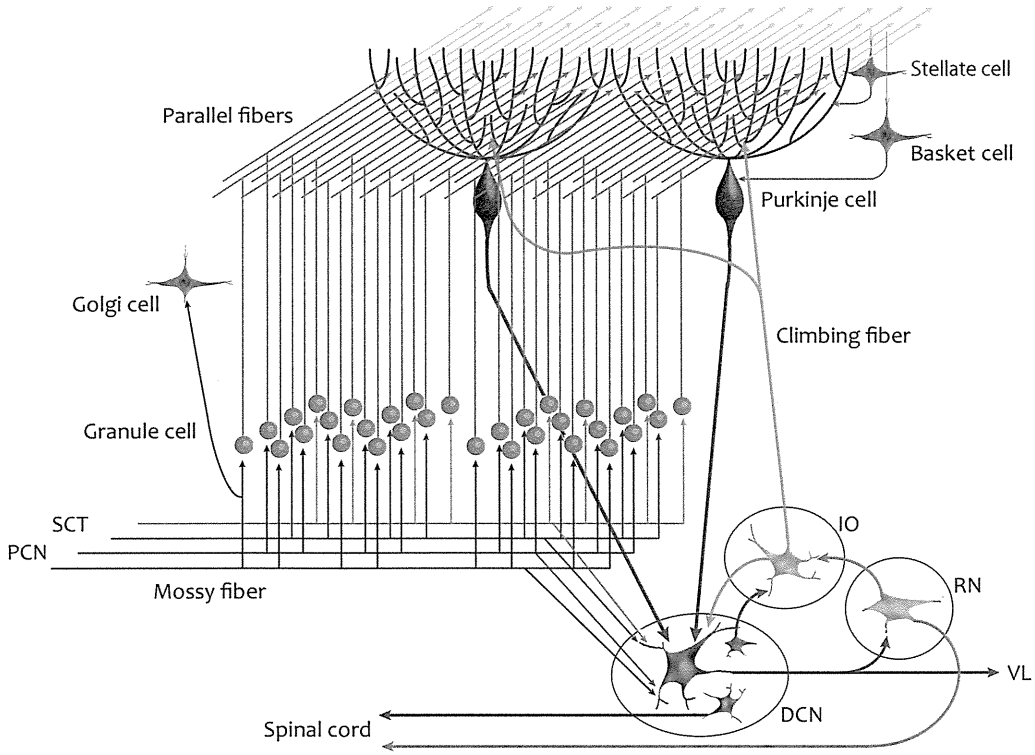


Figure 1 Schematic representation of the neuronal circuit of the cerebellum. The cerebellum contains numerous modules, each consisting of uniformly structured neuronal circuits. There are two main afferent pathways to the cerebellar cortex: mossy fibres, which terminate in the granular layer and form excitatory synaptic contacts mainly with granule cells (but also with Golgi cells), and climbing fibres, which form direct excitatory contacts with Purkinje cells. The stem axons of climbing and mossy fibres also provide collateral to the cerebellar deep nuclei. The ascending axons of the granule cells branch in a T-shaped manner to form parallel fibres, which form excitatory synaptic contacts with Purkinje cells (and molecular layer interneurons, stellate cells and basket cells). With the exception of granule cells, all cerebellar cortical neurons, including the Purkinje cells, form inhibitory synaptic connections with their target neurons. DCN, deep cerebellar nucleus; IO, inferior olive; RN, red nucleus; PCN, precerebellar nucleus; SCT, spinocerebellar tracts; VL, ventrolateral thalamus.

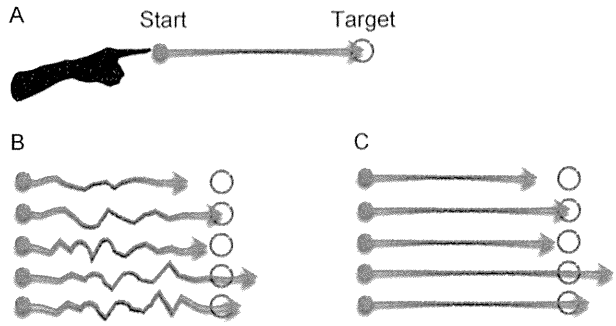


Figure 2 Hand trajectories in a straight-line motion towards a target. (A) Healthy individuals can move their hand smoothly along a straight line towards the target. (B) A defect in the cerebellar cortical neurons including Purkinje cells causes malformation of the cerebellar internal models, consequently leading to uncoordinated, irregular movements, such as decomposition and dysmetria, in a straight-line motion. (C) A defect in afferents to the cerebellar cortex via mossy fibres results in mis-selection of the internal model. This mismatch between the proper internal model and actual body dynamics typically results in dysmetria.

system can predict the consequence of an action and selects the ideal internal model for the given purpose.[3–7 10 14 21]

Information about a body part in space is mainly conveyed by the vestibulopontine pathway or spinocerebellar system through the inferior cerebellar peduncle via mossy fibres (some information from spinal cord via superior cerebellar peduncle). The vestibulocerebellar system conveys information about the situation and location of the head from the vestibular nucleus to the vestibulocerebellum (flocculonodular lobe).[21] This lobe also receives information from the superior colliculus and the posterior lobe, which contributes to the stability of the head in space, accompanied by visual information. The spinocerebellar system conveys proprioceptive information about peripheral areas of the body from the spinal cord to the spinocerebellum (vermis and paravermis).[21 23 24] Therefore, any disturbance in these regions has an ataxic effect on actions that require feedback information from the head or other parts of the body.

CLARKE'S COLUMN: A CENTRE FOR LOCOMOTION AND STANCE?

One of the regions frequently involved in spinocerebellar ataxias (SCAs) is Clarke's column, which is located in the dorsolateral part of the T1–L2 spinal cord.[23 24] It conveys proprioceptive information from the lower extremities and body to the ipsilateral cerebellum through the dorsal spinocerebellar tracts (figures 1 and 3A). Although the physiological function of this pathway is not fully understood, recent findings indicate that the neurons in Clarke's column have direct sensorimotor communication and receive information from the central pattern generator of the spinal cord, which generates rhythmic motor activity such as that used in locomotion.[23–25] These facts suggest that Clarke's column does not simply relay peripheral sensory information to the cerebellum, but it also acts as a centre for specific actions.[23–25] Information from the central pattern generator of the spinal cord may play a role in distinguishing sensory inputs that are a consequence of active locomotion from those attributable to perturbations in the external world.[26] Therefore, an abnormality of Clarke's column may contribute to gait disturbance in two ways: (1) interference with actions that compensate for perturbations in rhythmic movement, and (2) delivery of erroneous proprioceptive information from the body periphery.

For forelimb movement, the center for direct sensorimotir communication also exist in brainstem and spinal cord.[22 27 28] These circuits project to the cerebellum via mossy fibres and are associated with highly specific skilled forelimb movements, suggesting the existence of a centre for forelimb movement in these areas.[22 27 28]

THE CEREBELLAR DEEP NUCLEI: EFFERENT PATHWAY

Purkinje cells convey the results of analysis of afferent information somatotopically to neurons of cerebellar deep nuclei, including the fastigial, interposed and dentate nuclei (figures 1 and 3A).[9 15] Most of the output information from the cerebellum originates from the cerebellar deep nuclei. The number of neurons in the cerebellar deep nuclei is striking low relative to the number of Purkinje cells, and therefore these nuclei gather information from Purkinje cells.[15] It has been speculated that the cerebellar deep nuclei are related to the control of timing, rather than modality or topography,[17 29] and these interposed nuclei consolidate procedural memory.[16] Interestingly, perturbation of the cerebellar deep nuclei has been reported to be responsible for the postural instability seen in patients with metronidazole intoxication and progressive supranuclear palsy.[30] Disturbance of the outflow pathway from the cerebellar deep nuclei, or the thalamocortical or rubrospinal pathway, due to cerebrovascular accidents sometimes causes severe postural instability or intentional tremor in the upper extremities.

Although the structure of the cortical circuit is identical in each part of the cerebellum, the input and output pathways differ according to the part. The Purkinje cells in the vermis and in the intermediate part of the cerebellar hemisphere receive sensory information from the spinal cord and brainstem mainly via inferior cerebellar peduncle (some information is received from the spinal cord via superior cerebellar peduncle).[21 23 24] Purkinje cells in the vermis send projections to the fastigial nucleus, which projects bilaterally to the reticular formation and lateral vestibular nuclei, followed by composing the medial reticulospinal tract and the lateral vestibule-spinal tract, respectively.[2 21] The pathways are important for movements of the head and neck, and for balance and postural control during voluntary motor tasks. Purkinje cells in the intermediate part of the cerebellar hemisphere project to the interposed nuclei, which in turn project to the contralateral red nucleus, followed by composing the contralateral rubrospinal tract. This pathway is important for integration of sensory input from body parts with given action to adjust postures or movements to environments.[9 10 12 24]

In contrast to other cerebellar regions, the lateral hemispheres receive afferent signals exclusively from the cerebral cortex via the pontine nucleus.[10 21 31] Purkinje cells in the lateral cerebellar hemispheres project to the dentate nucleus, which is markedly enlarged in humans. The nucleus projects to both the contralateral ventrolateral thalamus and red nucleus. The parvocellular red nucleus, the part receiving inputs from the dentate nucleus, projects to the inferior olivary nucleus, which projects and terminates to Purkinje cells in the contralateral cerebellum, thus forming a feedback loop.[29] The efferent pathways via the dentate nucleus are responsible for the planning, initiation and control of well-trained voluntary movements.[17 29]

Purkinje cells in the flocculonodular lobes, which receive input from the vestibular nuclei and superior colliculi, directly provide output to the medial and lateral vestibular nuclei in the brainstem.[21] The efferent pathway via the lateral vestibular nucleus controls axial muscles and limb extensor muscles, stabilising balance during standing and walking. The efferent

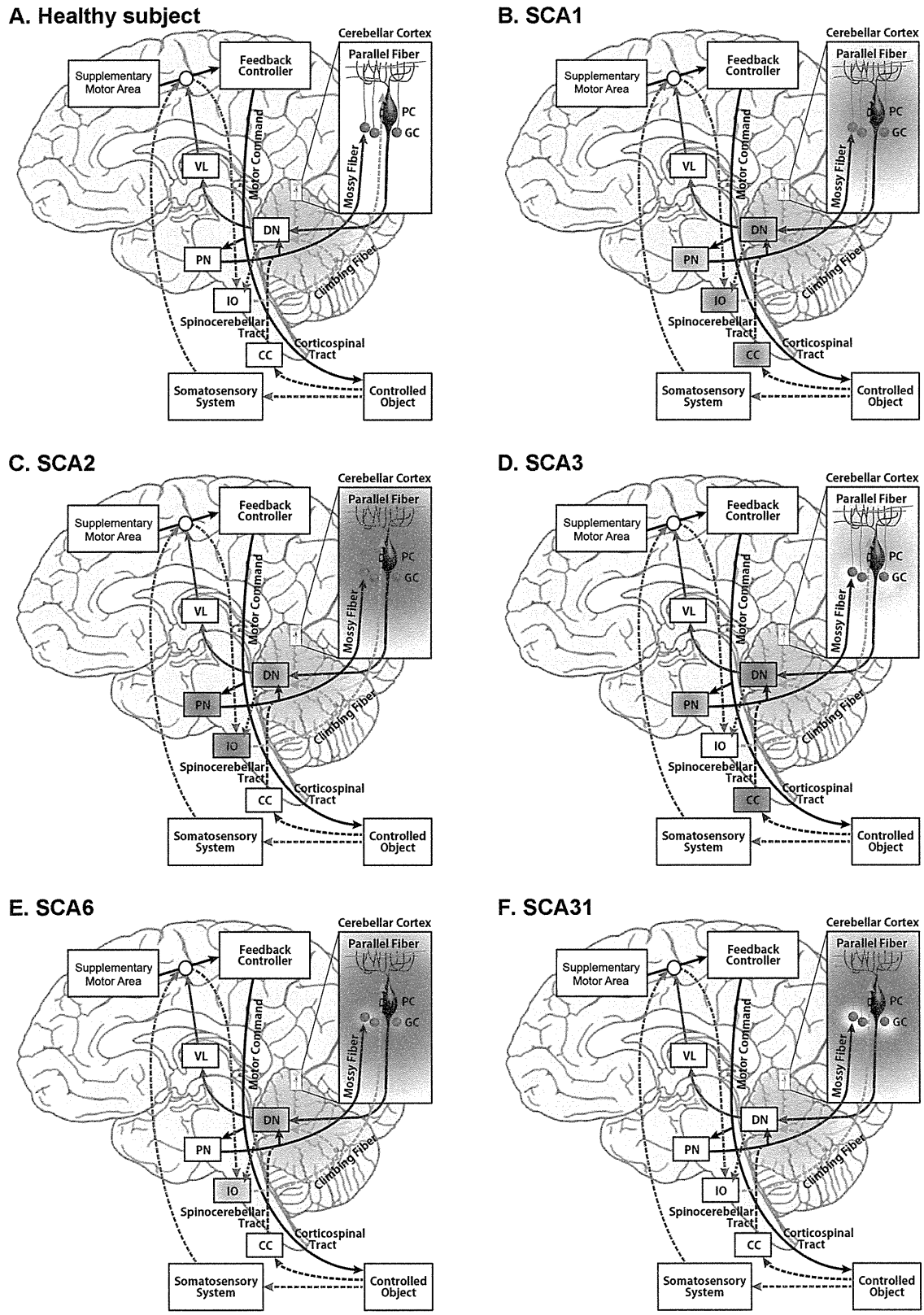
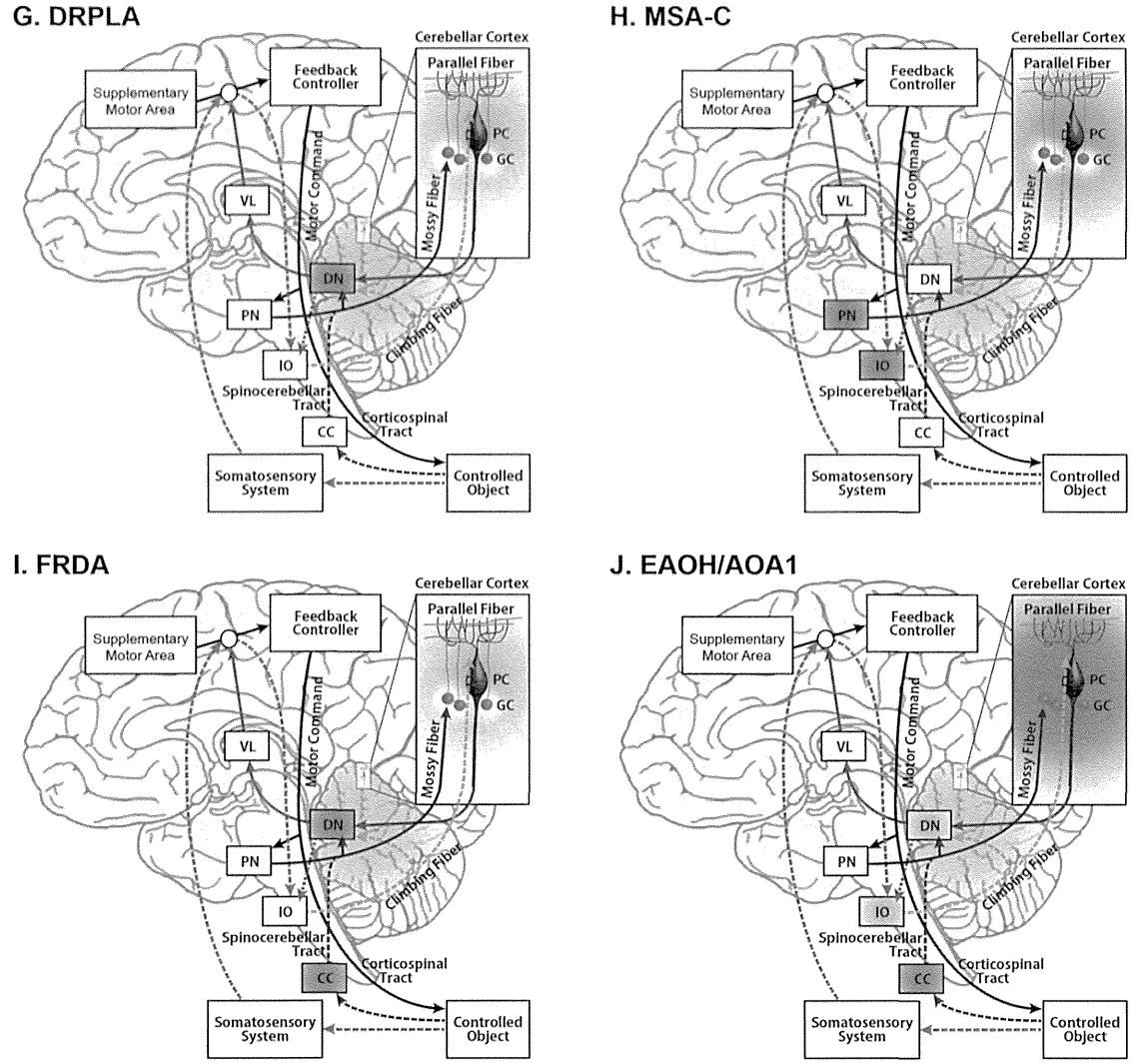


Figure 3 Distribution of neurodegeneration in the brain of patients with spinocecerebellar ataxias. (A) Healthy subjects, neuroal circuit for cerebellar system. (B) SCA1, spinocerebellar ataxia type 1. (C) SCA2, spinocerebellar ataxia type 2. (D) SCA3, spinocerebellar ataxia type 3. (E) SCA6, spinocerebellar ataxia type 6. (F) SCA31, spinocerebellar ataxia type 31. (G) DRPLA, dentatorubro-pallidoluysian atrophy. (H) MSA-C, multiple system atrophy-cerebellar type. (I) FRDA, Friedreich's ataxia. (J) EAOH/AOA1, early-onset ataxia with ocular motor apraxia and hypoalbuminaemia/ataxia with ocular motor apraxia type 1. (B)-(J) The degree of neurodegeneration in the anatomical regions related to the cerebellar systems is indicated by red (severe) or light red (moderate, or mild) colouration. (K) Summery of distribution of neurodegeneration in each degenerative ataxia, +++, severly affetced; ++, moderately affected; +, mildly affected; –, reratively spared. CC, Clarke's column; DN, dentate nucleus; DRG, dorsal root ganglia; IO, inferior olive; GC, granule cell; PC, Purkinje cell; PN, pontine nucleus; RN, red nucleus; VL,ventrolateral thalamus; VN, vestibular nucleus.



K. Summary of distribution of neurodegeneration in each degenerative ataxia

Disease	DRG	CC	VN	PN	GC	PC	DN	RN	IO
DRPLA	−	−	−	−	−	+	+++	+	−
SCA6	−	−	−	−	+	+++	++	−	+
SCA31	−	−	−	−	−	+++	−	−	−
MSA	−	−	+	+++	−	+	−	−	+++
SCA2	−	−	++	+++	+++	+++	++	+	+++
SCA1	−	++	+	+	++	++	++	−	++
SCA3	−	+++	++	++	−	+	+++	−	−
FRDA	+++	+++	++	−	−	+	+++	−	−
EAOH	+++	+++	−	−	+	+++	+	−	+

Figure 3 Continued.

pathway via the medial vestibular nucleus controls eye movements, and adjusts movements of the head and eyes.[29]

THE INFERIOR OLIVES: A SUPERVISION OF CEREBRAL CIRCUITS

The olivary nucleus, as well as the dentate nucleus and cerebellar hemisphere, is very well developed in humans, suggesting that this system may play an important role in actions that are characteristic of humans, such as hand movement, gait and speech. Neurons from the inferior olive send several climbing fibres to Purkinje cells and each fibre forms numerous synaptic contacts with the dendrites of a single Purkinje cell.[2] Signals from climbing fibres induce long-term depression (LTD) in conjunctively activated parallel fibre–Purkinje cell synapses.[13] LTD in these synapses forms the basis for motor learning in the cerebellum. Long-term potentiation, the long-lasting increase of

synaptic strength, is the opposing process to LTD. It occurs in parallel fibre–Purkinje cell synapses when parallel fibres are stimulated at high frequency, without being paired with climbing fibre activation.[32]

The inferior olives receive signals from the cerebellar deep nuclei, spinal cord and cerebrum. Although the precise physiological function of the inferior olive is still controversial, it may function as a comparator and send teaching signals representing errors to Purkinje cells via the climbing fibres.[10] This error learning based on teaching signals would be a plausible basis for motor learning in the cerebellum.[14 33]

Inactivation of the inferior olive nuclei in cats has been shown to not cause limb ataxia immediately[34]; limb ataxia develops over the course of several months without any degeneration of Purkinje cells or the cerebellar deep nuclei. These results reveal that loss of the inferior olives affects limb movement in a long-term manner, supporting the hypothesis that climbing fibres convey teaching signals. Erroneous teaching signals or lack of prompt feedback from actions may prevent effective reformation of internal models or lead to formation of erroneous models in the cerebellar circuit. However, several studies have demonstrated that LTD in parallel fibre–Purkinje cell synapses is not necessarily needed for motor learning.[35 36] Impulses from climbing fibres are regular and have a low frequency, unlike those from parallel fibres, suggesting that only a specific type of impulse is suitable as a teaching signal.[36] Therefore, it is still unclear whether the major function of the inferior olive is transmission of teaching error signals. Another hypothetical function of the inferior olive is as a generator of timing[17 36]; it may possess a set of system properties that allow temporal or rapid correction of action in response to unexpected events.

REDEFINING CEREBELLAR ATAXIA IN THE CONTEXT OF CEREBELLAR SYSTEM FUNCTION

With regard to its relationship with the internal models, we attempt to classify cerebellar ataxia into two categories: ataxia caused by a malformation of internal models and ataxia caused by mis-selection of internal models. Loss of cerebellar cortical neurons, involving Purkinje cells, may create inappropriate internal models,[1 2 4–6 9–13 15] resulting in uncoordinated irregular movements, such as decomposition and dysmetria, in the trajectory comprising a specific action (figures 1 and 2A,B). Input of incorrect afferent information to the cerebellum via mossy fibres from the cerebropontine pathway or the spinocerebellar or vestibulocerebellar systems may result in mis-selection of internal models.[23–26] This in turn could result in erroneous estimation of a desired action, represented as dysmetria, or increased variability of each interval in a repeated set of movements, represented as dysrhythmia (figures 1 and 2A,C). Although it has been proposed that the cerebellar ataxia are improved by the repeated manoeuvre, it would be interesting to investigate whether the accuracy and smoothness in the action are improved by the repeated manoeuvre in the situations with disturbance of afferent information system.

The corticopontocerebellar system is associated with skilled limb movements,[10 18 19] whereas the spinocerebellar or vestibulocerebellar system is associated with actions that require continuous feedback information, involving standing or gait.[12 15 20–22] The difference in the action contributed by each afferent information system in the cerebellum is well supported by the ataxia arising from cerebral infarction in each system. The damage to the corticopontocerebellar system at the pontine base causes dysarthria or clumsy hand syndrome in the contralateral side, which includes dysarthria; clumsiness, awkwardness and retarded fine movements of the affected hand; and difficulty in writing; however, a wavering ataxia on the finger–nose test is not clearly cerebellar in type.[18 19] In addition, Schmahmann *et al*[18] reported that dysmetria occurs in the ipsilateral side when the hemipontine lesion is extensive and interrupts pontocerebellar fibres traversing from the opposite side of the pons. Dorsolateral medullary infarction involves the dorsal spinocerebellar tract and the inferior cerebellar peduncle, which convey afferent information from the ipsilateral body and results in an ataxic gait.[20]

Degenerative ataxias are progressive neurodegenerative diseases involving the cerebellum as well as the brainstem, spinal cord and cerebrum.[37 38] Although degenerative ataxias involve several systems in the central nervous system (CNS), the distribution of the pathological lesions is unique to each degenerative ataxia. The regions of cerebellar circuits that are primarily affected in degenerative ataxias are summarised in figure 3A–K.[37 38] Based on knowledge about neuropathological findings in degenerative ataxias and the function of the cerebellar circuit, degenerative ataxias can be classified into four types based on the anatomical regions affected: Purkinje cells, the corticopontocerebellar system, the spinocerebellar system and the cerebellar deep nuclei (figure 3).

The neuropathological involvement in SCA31 is relatively restricted to Purkinje cells (figure 3F),[37] which may result in coarse internal models. Patients with SCA31 often show scanning speech and decomposition, which represent loss of smooth movement. However, because the patients' afferent and efferent systems are mostly preserved, it may be possible for them to reconstruct a new internal model using their residual cerebellar cortical circuits if correct movements are undertaken carefully and repeatedly. Indeed, patients with pure cerebellar ataxia respond well to rehabilitation, and this effect persists for more than several months.[39] In advanced stages, individuals with marked depletion of Purkinje cells lose their acquired internal models and are unable to learn a new internal model, resulting in marked ataxia. Although Purkinje cells are also predominantly involved in SCA6, degeneration of granule cells, inferior olive neurons and the dentate nucleus is evident (figure 3E).[37 38] Therefore, patients with SCA6 show more severe ataxia than those with SCA31.

In contrast, the disturbance of afferent systems involving the corticopontocerebellar or spinocerebellar system may disturb the selection of an appropriate internal model. Cerebellar-type multiple system atrophy (MSA-C) and SCA2 predominantly affect the pontine nuclei, which are involved in the corticopontocerebellar system and the inferior olives (figure 3C,H).[37 38] In the early stages of disease, disturbance of the pontocerebellar system may hinder selection of a proper internal model for well-trained limb movements in writing or playing instruments,[10 18 19] while an action that depends on the spinocerebellar tract might be relatively preserved at their onset.[12 15 20–22] Thereafter, however, the internal models might become progressively disordered because of erroneous information from the cerebral cortex. Furthermore, involvement of the inferior olive could disturb internal models in response to teaching error signals, leading to ataxic symptoms.

SCA1, SCA3, Friedreich's ataxia (FRDA) and early-onset ataxia with ocular motor apraxia and hypoalbuminaemia/ataxia with ocular motor apraxia type 1 (EAOH/AOA1) involve Clarke's column (figure 3B,D,I,J).[37 38] In these disorders, patients receive incorrect afferent information from somatosensory systems. Indeed, these patients show marked disability in

stance and gait that requires continuous feedback information from the body periphery.[12 15 20–22] Increasing the intensity of input signals from the lower limbs may stabilise these actions. It has been well recognised that heavily weighted shoes are of some benefit for correcting the disabilities of stance and locomotion seen in patients with ataxia. However, this approach would not be useful for diseases involving the corticopontocerebellar system, rather than the spinocerebellar system.

Dentatorubral-pallidoluysian atrophy mainly affects the outflow system without marked involvement of Purkinje cells (figure 2G).[37] Severe neuronal loss is evident in the dentate nucleus, with mild degeneration in the red nucleus. Degeneration in the dentatorubral system is relatively marked in cases with onset in late adulthood, while degeneration in the pallidoluysian system is relatively marked in juvenile cases.[37] SCA3 and FRDA also involve the dentate nucleus.[37] Involvement of the efferent system of the cerebellum may hamper its overall function, resulting in marked postural instability as well as limb ataxia.[16 30]

PERSPECTIVES

The degenerative ataxias also involve the cerebrum, brainstem and peripheral nervous system. For example, the medial and lateral vestibular nuclei are also involved in SCA2, SCA3, FRDA and MSA, resulting in marked disability in stance and gait.[37 38] Furthermore, degeneration of a part of cerebellar system may also cause degeneration in other parts of the cerebellum. In addition, the cerebellum is connected with other parts of the CNS, including the basal ganglia.[31] Therefore, these multiple reciprocal interconnections within the cerebellar system and other CNS structures may cause ataxias in each disease rather than an isolated disruption of individual structures and/or pathways in the cerebellum. Although we do not deny this possibility and we understand the difficulty in detailing the neurophysiological background in each disease, we would like to emphasise the need to interpret the ataxia within the proposed framework. The recent finding of differing speech characteristics in SCA3 and SCA6 supports our hypothesis.[40] SCA3 was found to have an increased temporal variability in syllable repetition compared with SCA6. In contrast, speech rate and prosody were more severely affected in SCA6 than in SCA3. Our approach to defining the characters of ataxias associated with each disorder may lead to the development of new rating instruments for evaluating degenerative ataxias in future.

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Redefining cerebellar ataxia in degenerative ataxias: lessons from recent research on cerebellar systems

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Neural Substrates of Cognitive Subtypes in Parkinson's Disease: A 3-Year Longitudinal Study

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Abstract

Background: The neuropsychological features and neuropathological progression patterns associated with rapidly evolving cognitive decline or dementia in Parkinson's disease (PD) remain to be elucidated.

Methods: Fifty-three PD patients without dementia were recruited to participate in a 3-year longitudinal cohort study. The patients were grouped according to the Clinical Dementia Rating (CDR). Group-wise comparisons were made with regard to demographic characteristics, motor symptoms, neuropsychological performances and 18F-fluorodeoxyglucose positron emission tomography.

Results: Patients who had memory-plus cognitive impairment (patients whose CDR was 0 at baseline and 0.5 in memory and other domains at follow-up, and those whose baseline CDR was 0.5 in memory and other domains) exhibited higher age at onset, visuoperceptual impairment, non-tremor-dominant motor disturbance, rapid symptomatic progression and posterior neocortical hypometabolism. In patients who were cognitively unimpaired and those who had memory-dominant cognitive impairment (patients whose CDR was 0 at baseline and 0.5 only in memory domain at follow-up, and those whose baseline CDR was 0.5 only in memory domain), the posterior neocortex was relatively unaffected until a later stage of the disease.

Conclusions: These results suggest that visuoperceptual impairment and the early involvement of the posterior neocortex may be risk factors for rapid symptomatic progression and dementia in PD.

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Introduction

The cognitive features of Parkinson's disease (PD) are heterogeneous and can be categorized into several major subtypes. [1,2] However, the neural substrates underlying the cognitive subtypes remain to be elucidated. Recent studies have demonstrated that there are correlations between cognitive impairment and non-cognitive features in PD: patients who develop dementia have a higher age of onset, rapid symptomatic progression, anosmia and a non-tremor-dominant motor subtype. [3,4,5,6] Consistent with these observations, neuropathological studies have suggested that the anatomical distribution of Lewy-related pathology differs depending on the clinical subtypes. The pathology rapidly evolves from the brainstem into the cerebral cortex in patients with the non-tremor-dominant motor subtype and/or dementia, whereas it is relatively confined to the brainstem for a longer period of time in patients with a tremor-dominant motor subtype and no cognitive impairment. [7] If such provisional clinico-pathological relationships are genuine and if specific subtypes of cognitive impairment are associated with the future development of dementia, these cognitive subtypes may be associated with specific clinico-pathological subtypes.

Previous morphometric MRI and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) studies have demonstrated greater frontal, temporal and occipital gray matter volume reduction and greater frontal and parietal cortical hypometabolism in PD patients with dementia or mild cognitive impairment (MCI) compared with cognitively unimpaired patients. [8,9,10,11,12] In agreement with these neuroimaging findings, several neuropathological studies demonstrated the relationship

between dementia and limbic and/or neocortical neurodgeneration. [13,14,15] However, there is only a little evidence for neuroimaging features predictive of later development of dementia and for distinctive progression patterns of cortical lesions among the PD subtypes. The sole previous longitudinal FDG-PET study of PD demonstrated that patients who developed dementia 1 to 3 years later exhibited occipito-parietal hypometabolism at baseline. [16] To further address this issue, we investigated the relationship among cognitive subtypes, other clinical features and changes in regional brain glucose metabolism (CMRglc) over 3 years in a cohort of PD patients.

Methods

All procedures in this study followed the clinical study guidelines of Tohoku University Hospital and were approved by its ethics committee. The patients gave written informed consent after receiving a detailed explanation of the study. When the patients had a compromised ability to consent, their family members gave consent on behalf of the patients.

Subjects

We analyzed 55 patients with PD without dementia (mean age 65.4±6.5 years; 27 women) who participated in a 3-year longitudinal study at Tohoku University Hospital. Details of the study design have been described elsewhere. [3,9,17] Briefly, outpatients at the movement disorder clinic who met the following criteria were recruited in the study: fulfillment of the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank; aged 50 years or more; absence of dementia according to the Diagnostic Statistical Manual-IIIR [18] and a Clinical Dementia Rating (CDR) [19] overall score of 0 or 0.5, no evidence of diabetes mellitus; no history of other neurological or psychiatric diseases; and no evidence of infarcts, bleedings, tumors and other focal brain lesions on MRI. Of 88 consecutive patients, 33 patients dropped out for the following reasons: 4 patients died; 4 were institutionalized; 1 developed psychosis; 2 developed myocardial infarction or cerebral infarction; 9 moved to hospitals near their homes; 6 did not return for follow-up visits for unknown reasons; the initial diagnosis of PD was dismissed in 3 patients; and 4 were excluded because of incomplete clinical or imaging data. Fourteen healthy volunteers (mean age 63.1±4.4 years; 6 women) were recruited as controls for neuroimaging. There were no significant differences in age ($t = 1.6$, $p = 0.1$) or sex ($x^2 = 0.2$, $p = 0.7$) between the patient and control groups.

Comparison of patient classification procedures: the neuropsychology-based criteria versus the Clinical Dementia Rating

Measuring cognitive changes is challenging because there is no very reliable change measures. Practice effects associated with the repeated administration have a great impact on neuropsychological test performance, yielding spurious cognitive improvement over time. [20,21,22,23] A recent study demonstrated that previous test exposures lead to bias towards normal cognition in the diagnosis of MCI. [24]In addition, cognitive assessment in PD is complicated by motor symptoms, such as bradykinesia and tremor, and medication-related effects. [2] To take these problems into account, global cognitive measures and/or caregiver interviews have been used in longitudinal intervention trials for cognitive disorders. [25,26,27,28] According to this convention, we have introduced the CDR, a global cognitive measure based on examinations by clinicians and caregiver interview, in our cohort study of PD. [3,9,17] To examine the rationality of the use of the CDR in the classification of cognitive status in PD, we compared the 3-year cognitive changes based on the neuropsychology-based criteria for MCI in PD (PD-MCI) and those based on the CDR in the patients (n = 46) who completed neuropsychological tests for memory, visuoperceptual ability and attention/working memory (see below for the details of the neuropsychological tests). PD-MCI was defined according to the Movement Disorder Society Guideline for PD-MCI Level I (MDS PD-MCI criteria), in which the diagnosis of PD-MCI required impairments of 1 to 2 standard deviations (SDs) below norms on at least 2 neuropsychological tests. [29] In the CDR-based criteria, the patients were classified as CDR 0 (unimpaired cognition) or CDR 0.5 (cognitive impairment which mildly affecting their everyday life).

Patient classification based on the Clinical Dementia Rating

The CDR, which was designed to provide a rating scale for subjects from normal cognition through various stages of dementia, is widely considered to be a reliable scale for staging the severity of cognitive dysfunction. [19] The CDR comprises 6 subdomains, i.e., memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. In matters related to the domains of community affairs, home and hobbies, and personal care, we asked the patients and their caregivers about cognition-related functional decline separately from disability arising from physical impairment in order to eliminate as far as possible the effects of non-cognitive symptoms. [9,17].

The primary aim of the current study is to discover clinical features and distinctive brain metabolic patterns of patients who have rapid cognitive deterioration. To this end, we first focused on 40 patients who were cognitively unimpaired (CDR 0) at baseline. Among these patients, 26 patients were cognitively unchanged over 3 years (CDR 0 at the third year; non-converters), 7 worsened only in the memory domain (memory-only converters) and 6 worsened in the memory and non-memory domains (memory-plus converters). The remaining patient, who showed deterioration only in a non-memory domain, was excluded from the analyses. Second, we analyzed patients whose overall CDR scores were 0.5 at baseline to investigate longitudinal brain metabolic changes after PD patients developed mild cognitive deficits. Eight patients who scored ≥0.5 only in the memory domain at baseline (baseline memory-only) and 6 patients who scored ≥0.5 in the memory and other domains (baseline memory-plus) were recruited for the study. We speculated that the baseline memory-only and the baseline memory-plus patients may represent the clinico-pathological stages following the memory-only converters and the memory-plus converters, respectively. We conducted group comparisons separately among the groups of baseline CDR 0, specifically non-converter, memory-only converter and memory-plus converter patients, and between the groups of baseline CDR 0.5, specifically baseline memory-only and baseline memory-plus patients, because our interest was in longitudinal changes in clinical symptoms and brain glucose metabolism.

Cognitive and motor assessments

The Mini-Mental State Examination (MMSE) and the Word Recall subtest of the Alzheimer's Disease Assessment Scale (ADAS) were used to assess general cognitive function and episodic memory, respectively. [30,31] Visuoperception was assessed using the correct response score on the overlapping-figure identification test. [32] A subset of patients underwent the backwards digit-span test to assess their working memory (the number of patients is indicated in **Tables 1 and 2**). [29] Further

details have been described elsewhere. [17,32] Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III. We calculated the rate of progression indices for the clinical measures described above using the following formula: (rate of progression) = [(third year score)-(baseline score)]/(years of interval). [33] The tremor and non-tremor motor scores were calculated based on the UPDRS parts II and III. [5].

Statistical analyses

Group-wise comparisons of demographic data and baseline scores and progression rates of the cognitive and motor measures were analyzed using the statistical methods described in the captions of **Tables 1 and 2**. Two-way repeated-measures analysis of variance (ANOVA) with motor subtypes (the tremor and non-tremor scores of UPDRS) and time (baseline and third year) was performed to characterize the motor features of the groups. To enable comparisons with previous studies in which cognitive subtypes were determined by neuropsychological test scores, we investigated the number of patients whose scores were 1 SD or more below the mean of normative data for the ADAS-word recall, overlapping figure and backwards digit-span tests.

18F-fluorodeoxyglucose positron emission tomography

The mean interval between the clinical assessments and the positron emission tomography (PET) scan was 4.6 days. Each patient had fasted, and dopaminergic medication had been discontinued for at least 5 hours before the scan. Scanning was performed after an injection of 185–218 MBq 18F-fluorodeoxyglucose (FDG). After an FDG-uptake period of 1 hour, a 20-minute scan was acquired while the patient was at rest. Details of the scanning procedures have described elsewhere. [17,32] Image pre-processing and statistical analysis were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). All images were normalized onto the standard FDG template with nonlinear warping algorithms, reconstructed into 2 mm^3 isotropic voxels and smoothed with 10 mm full width at half-maximum. Global normalisation was performed using proportional scaling, and threshold masking was set at 0.8. Cross-sectional comparisons between the patient groups and the controls were performed using *t*-test. Two-way repeated-measures ANOVA was used for cross-sectional and longitudinal comparisons of the patient groups. Age and sex were included as nuisance variables in all of the comparisons. The UPDRS part III score was included as a nuisance variable in the comparisons among the patient groups. The statistical threshold was set at an uncorrected $p<0.001$ at the voxel level and at 20 voxels at the cluster level.

Results

Comparison between the neuropsychology-based criteria and the Clinical Dementia Rating-based criteria

The results are summarized in **Figure 1.** The neuropsychology-based classification according to the MDS PD-MCI criteria exhibited a spurious improvement over 3 years in 5 of the 12 patients who were classified to PD-MCI at baseline, whereas such an effect was observed only in 1 of the 11 patients who scored 0.5 on the baseline CDR (**Figure 1**). Based on these preliminary findings, we decided to employ the CDR-based cognitive criteria in the current study.

Clinical profiles of the patient groups of baseline Clinical Dementia Rating 0

The results are summarized in **Table 1**. There were no significant differences among the non-converters, memory-only converters and memory-plus converters in sex, education, disease duration, levodopa equivalent dose or test-retest interval. The memory-plus converters had a significantly higher age of onset and a higher age at baseline than did the non-converters.

Baseline performance of the overlapping figure test was lower in the memory-plus converters than in the non-converters ($F = 10.1$, $p<0.001$). The baseline performance of the backwards digit-span was worse in the memory-only converters than it was in the non-converters ($F = 7.1$, $p<0.01$). No group differences were observed in baseline MMSE or baseline ADAS word recall. There were no significant differences in the progression rate on any of the cognitive tests.

No significant difference was observed in the baseline UPDRS part III among the three groups. The progression rate of the UPDRS part III was greater in the memory-plus converters than it was in the non-converters and the memory-only converters ($F = 6.8$, $p<0.01$). The UPDRS non-tremor score was higher in the memory-plus converters than it was in the other groups ($F = 18.8$, $p<0.001$), and no significant main effect of time or interaction between motor subtypes and times was observed.

Clinical profiles of the patient groups of baseline Clinical Dementia Rating 0.5

The results are summarized in **Table 2**. There were no significant differences between the baseline memory-only and the baseline memory-plus patients in age at baseline, sex, education, age of onset, disease duration, levodopa equivalent dose or test-retest interval. No significant group differences were observed in the baseline scores or progression rates on any of the cognitive tests. No significant difference was observed in the baseline UPDRS part III score. The UPDRS part III progression rate was greater in the baseline memory-plus patients than it was in the baseline memory-only patients ($t = -2.4$, $p<0.05$). The UPDRS non-tremor score was higher in the baseline memory-plus patients than it was in the baseline memory-only patients ($F = 8.0$, $p< 0.001$).

Positron emission tomography: comparisons between patient groups and controls

Compared with the controls, the non-converters and memory-only converters exhibited patchy, discrete areas of hypometabolism in the frontal, temporal and occipital cortices at baseline (**Figures 2A and 2B**). The memory-plus converters showed extensive hypometabolic areas in the temporo-parietal and occipital cortices compared with the controls (**Figure 2C**).

The regional pattern of metabolic reduction relative to the controls was similar among the baseline memory-only patients, the non-converters and the memory-only converters (**Figure 2D**). The baseline memory-plus patients showed a similar but more extensive hypometabolism compared with the memory-plus converters, in whom the metabolic reduction relative to controls was greatest in the temporo-parietal and medial parietal cortices (**Figure 2E**).

Positron emission tomography: comparisons among the patient groups of baseline Clinical Dementia Rating 0

At baseline, there was no significant difference in regional glucose metabolism between the non-converters and memory-only converters (**Figure 3A**). The memory-plus converters showed a

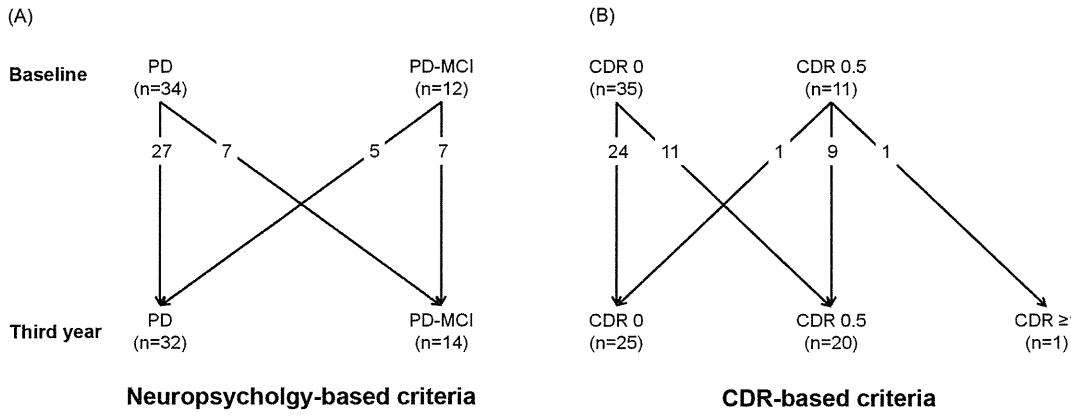

Figure 1. Diagrams of the 3-year cognitive changes observed in patients. In (A), the patients were classified as having Parkinson's disease without cognitive impairment (PD) or PD with mild cognitive impairment (PD-MCI) based on neuropsychological tests. (B) shows the results based on the Clinical Dementia Rating (CDR)-based patient classification.
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stronger metabolic reduction in the parietal and occipital cortices compared with the non-converters and amnesic converters at baseline (**Figures 3B and 3C**).

The non-converters showed a significant metabolic decline over 3 years in the frontal, temporal, medial parietal and occipital cortices and the thalamus (**Figure 4A**). In the memory-only converters, regional glucose metabolism was decreased in the anterior cingulate cortex, medial temporal lobe, caudate nucleus and midbrain over 3 years (**Figure 4B**). No significant longitudinal metabolic change was observed in the memory-plus converters (**Figure 4C**). An ANOVA interaction demonstrated that metabolic decline over 3 years in the medial temporal lobe was greater in the memory-only converters than it was in the non-converters (**Figure 4F**).

Positron emission tomography: comparisons between the patient groups of baseline Clinical Dementia Rating 0.5

The baseline memory-only patients had lower baseline regional glucose metabolism in the medial temporal lobe, cingulate cortex and dorsal brainstem regions than did the baseline memory-plus patients, whereas the regional glucose metabolism in the temporo-parietal and medial parietal cortices was lower in the baseline memory-plus patients than it was in the baseline memory-only patients (**Figures 3D and 3E**).

Regional glucose metabolism was decreased over 3 years in the parietal cortex in the baseline memory-only patients, whereas a longitudinal metabolic decline was observed in discrete regions of the basal forebrain and the brainstem in the baseline memory-plus patients (**Figures 4D and 4E**). An ANOVA interaction revealed circumscribed ventral frontal and basal forebrain regions that showed a greater 3-year metabolic decline in the baseline memory-plus patients than in the baseline memory-only patients (**Figure 4G**).

Discussion

Early visuoperceptual impairment and posterior cortical hypometabolism may represent the clinical subtypes of rapidly progressive motor symptoms and severe cognitive impairment

The clinical entity of PD encompasses a wide variety of symptoms, including motor, sensory, cognitive and autonomic disturbances. Recent cluster-analysis studies have suggested that two major clinical subtypes can be extracted from the clinical diversity: one subtype is characterized by a young age of onset, slow disease progression, tremor-dominant motor features and preserved cognition, and the other is associated with an older age of onset, rapid disease progression, non-tremor-dominant motor features and cognitive impairment. [5,6,34] In parallel with these discoveries, there has been growing evidence of the neuropathological diversities underlying these clinical subtypes. Patients with a young age of onset, slow progression and tremor-dominant motor features are reported to have neuropathological features that conform to Braak's pathological staging scheme, in which Lewy-related pathology begins in the lower brainstem (stages 1–2); ascends to the midbrain (stage 3), thalamus and limbic structures (stages 4); and finally reaches the neocortex (stages 5–6). [35] By contrast, patients with an older age of onset, non-tremor-dominant motor features and/or dementia are associated with disproportionately severe neocortical Lewy-related pathology and concomitant Alzheimer's disease-related pathology. [14,15].

In the current study, the memory-only converters showed a metabolic decline over 3 years in the anterior cingulate and medial temporal cortices (**Figure 4B**). The baseline memory-only patients, whose baseline cognitive status was similar to that of the memory-only converters at the third year, showed a metabolic decline in the parietal cortex (**Figure 4D**). Assuming that these patient groups represent a single cognitive subtype at different time points, these results suggest that neurodegeneration first affects the limbic structures and next encroaches on the posterior neocortex. This pattern of brain metabolic changes is largely consistent with Braak's scheme. [7] A longitudinal PET analysis of the non-converters demonstrated 3-year metabolic decline in the thalamus and occipital cortex (**Figure 4A**). A direct comparison between the non-converters and the memory-only converters revealed no significant group difference at baseline but greater metabolic decline over time in the memory-plus converters than in the non-converters (**Figures 3A and 4F**). These two groups of patients may represent slightly different subpopulations of a clinico-pathological subtype that conforms to Braak's scheme.

The memory-plus converters exhibited extensive posterior cortical hypometabolism at baseline compared with the controls and the non-converters (**Figures 2C, 3B and 3C**). Likewise, more extensive posterior cortical hypometabolism was observed in the baseline memory-plus patients compared with the baseline

Table 1. Demographic and clinical profiles of patients with a Clinical Dementia Rating of 0 at baseline.

		Non-converter (N = 26)	Memory-only converter (N = 7)	Memory-plus converter (N = 6)	Differences among groups
Age at baseline (years)		62.2±5.9	67.7±5.5	71.8±2.6	Memory-plus>Non-converters[b]
Gender (male/female)		12/14	2/5	1/5	
Education (years)		11.8±2.5	11.1±2.5	12.0±2.8	
Test-retest interval (days)		1140.2±110.7	1107.7±43.5	1109.7±59.7	
Disease duration at baseline (years)		4.3±3.7	5.0±6.9	5.0±3.2	
Age at onset (years)		58.0±7.3	63.6±6.0	67.2±5.4	Memory-plus>Non-converters[b]
Levodopa equivalent dose at baseline (mg/day)		303.5±233.1	378.9±320.4	533.6±340.2	
UPDRS part III	Baseline	18.0±7.3	18.9±8.0	16.5±6.2	
	Progression rate (/years)	−0.02±2.0	−0.8±0.8	4.0±5.2	Memory-plus>Non-converters[b]; Memory-plus>Memory-only[b]
UPDRS tremor score¶	Baseline	0.5±0.4	0.4±0.6	0.3±0.4	
	Third year	0.3±0.3	0.2±0.2	0.3±0.3	Main effect of non-tremor score: Memory-plus>Non-converters[b]; Memory-plus>Memory-only[b]
UPDRS non-tremor score ¶	Baseline	0.7±0.3	0.7±0.4	0.7±0.2	
	Third year	0.8±0.3	0.7±0.4	1.6±0.2	
CDR sum of boxes	Baseline	0	0	0	NE
	Third year	0	0.5	1.8±0.8	NE
MMSE	Baseline (/30)	28.2±1.8	27.3±2.6	27.5±1.9	
	Progression rate (/years)	0.1±0.6	−0.1±0.9	−0.6±0.7	
ADAS word recall†	Baseline (/30)	19.3±3.4	17.3±4.5	17.8±4.4	
	Progression rate (/years)	0.6±0.9	1.2±1.1	−0.03±1.2	
Overlapping figure‡	Baseline (/40)	33.4±4.0	29.6±2.4	25.3±6.3	Non-converters>Memory-plus[b]
	Progression rate (/years)	−0.2±1.0	0.7±0.9	−0.9±2.0	
Backward digit-span§	Baseline	4.4±0.8	3.0±0.9	4.0±0.7	Non-converters>Memory-only[a]
	Progression rate (/years)	−0.1±0.3	0.1±0.4	−0.2±0.2	
# of patients below −1 SD at baseline and at third year	ADAS word recall †	9/26 3/26	3/7 1/7	3/6 3/6	NE
	Overlapping figure‡	4/26 3/26	2/7 0/7	5/6 5/6	NE
	Backward digit-span§	1/25 5/25	4/6 4/6	1/5 3/5	NE

Analysis of variance with post-hoc Tukey's test was used for group-wise comparisons of baseline scores and progression rates except for the UPDRS tremor/non-tremor scores. Two-way analysis of variance with post-hoc Tukey's test was used for the UPDRS tremor/non-tremor scores. Data are given as the mean±SD except for the fields with asterisks. a and b indicate $p<0.05$ and $p<0.01$, respectively.

*Data are given as (the number of patients below −1 SD)/(the number of patients who underwent the test).

¶The scores were calculated according to Lewis and colleagues. [5] Data were obtained from 21 non-converters, 6 memory-only converters and 5 memory-plus converters.

†The mean score for controls (n = 20, 65.5±4.8 years) is 21.3±3.5. [49].

‡The mean score for controls (n = 24, 66.1±5.3 years) is 32.9±4.4. [32].

§The mean score for controls (n = 20, 65.5±4.8 years) is 4.8±1.0. [49].

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; NE, not examined.

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Table 2. Demographic and clinical profiles of patients with a Clinical Dementia Rating of 0.5 or more at baseline.

		Baseline memory-only (N = 8)		Baseline memory-plus (N = 6)		Differences between groups
Age at baseline (years)		69.0±6.6		66.2±5.5		
Gender (male/female)		6/2		6/0		
Education (years)		12.3±2.3		14.3±2.7		
Test-retest interval (days)		1115.3±107.1		1096.7±54.7		
Disease duration at baseline (years)		6.8±3.3		9.7±6.8		
Age at onset (years)		62.4±6.6		56.6±8.0		
Levodopa equivalent dose at baseline (mg/day)		453.6±163.1		658.6±337.9		
UPDRS part III	Baseline	27.1±5.4		23.8±6.6		
	Progression rate (/years)	−0.7±3.3		4.6±5.0		Baseline memory-plus>Baseline memory-only[a]
UPDRS tremor¶	Baseline	0.7±0.5		0.4±0.6		
	Third year	0.3±0.2		0.4±0.7		Main effect of non-tremor score: Baseline memory-plus>Baseline memory-only[a]
UPDRS non-tremor¶	Baseline	1.2±0.2		1.0±0.1		
	Third year	1.1±0.2		1.7±0.7		
CDR sum of boxes	Baseline	0.5		2.1±1.3		NE
	Third year	1.4±1.2		5.3±4.1		NE
MMSE	Baseline (/30)	27.0±3.0		27.0±2.2		
	Progression rate (/years)	−0.3±0.7		−1.1±2.7		
ADAS word recall†	Baseline (/30)	17.9±4.1		14.3±5.4		
	Progression rate (/years)	−0.1±1.4		−0.3±1.2		
Overlapping figure‡	Baseline (/40)	29.6±4.1		29.4±6.2		
	Progression rate (/years)	0.1±1.1		−2.4±3.1		
Backward digit-span§	Baseline	3.6±1.0		3.8±0.5		NE
	Progression rate (/years)	−0.1±0.1		−0.3±0.3		NE
# of patients below −1 SD at baseline and at third year	ADAS word recall†	4/8	3/8	5/6	5/6	NE
	Overlapping figure‡	3/8	4/8	2/5	5/5	NE
	Backward digit-span§	3/7	4/7	1/4	2/4	NE

Two-sample *t*-tests were used for group-wise comparisons of baseline scores and progression rates except for the UPDRS tremor/non-tremor scores. A two-way analysis of variance was used for the UPDRS tremor/non-tremor scores. No group-wise comparisons were performed for the backward digit-span owing to the small number of subjects. Data are given as the mean±SD except for the fields with asterisks. a and b indicate $p<0.05$ and $p<0.01$, respectively.

*Data are given as (the number of patients below −1 SD)/(the number of patients who underwent the test).

¶The scores were calculated according to Lewis and colleagues. [5] Data were obtained from 6 baseline memory-only and 6 baseline memory-plus patients.

†The mean score of controls (n = 20, 65.5±4.8 years) is 21.3±3.5. [49].

‡The mean score of controls (n = 24, 66.1±5.3 years) is 32.9±4.4. [32].

§The mean score of controls (n = 20, 65.5±4.8 years) is 4.8±1.0. [49]; a statistical comparison was not performed owing to an insufficient number of subjects.

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; NE, not examined.

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memory-only patients (**Figures 2E and 3E**). These findings can be interpreted in two ways: the posterior neocortical hypometabolism found in these patients may represent pathological changes in Braak stages 5–6, or they may represent a pathological progression pattern that does not conform to Braak's scheme. [7] The latter was suggested by the following clinical and neuroimaging findings. First, the severity of motor symptoms at baseline was equivalent in the memory-plus converters, non-converters and memory-only converters, suggesting that the three groups had similar degrees of midbrain pathology. In other words,