TABLE 3. Affected cortical regions in MSA assessed by different imaging procedures

	Frontal	Temporal	Parietal	Study
MRI VBM	• Left superior frontal region[a] • Left inferior frontal region[a] • Medial frontal region • Middle frontal region • Orbitofrontal cortex	• Right hippocampus • Right inferior temporal region • Insula • Hippocampus • Temporomesial- ventral enthorinal cortex	• Left posterior parietal cortex	9, 20[a], 46, 48, 49-51
FDG PET	• Dorsolateral prefrontal cortex[a] • Lateral frontal cortex (early)[a] • Medial frontal cortex (early)[a] • Orbitofrontal cortex	• Superior temporal region (advanced)[a] • Middle temporal region (advanced)[a] • Inferior temporal region (advanced)[a] • Fusiform gyrus (advanced)[a]	• Inferior parietal region • Left angular gyrus (advanced)[a] • Left precuneus (advanced)[a] • Right posterior cingulate cortex (advanced)[a]	12,[a] 26,[a] 55
^{99m}Tc-ECD SPECT	• Left lateral frontal region • Left prefrontal cortex • Right middle frontal region	• Insula (more pronounced on the left)		78, 79

[a]Evidence from comparative studies of cognitive impairment and its imaging correlates.
MRI, magnetic resonance imaging; VBM, voxel-based morphometry; FDG-PET, ^{18}F-fludeoxyglucose positron emission tomography; ^{99m}Tc-ECD SPECT, ^{99m}Technetium-ethyl cysteinate dimer single-photon-emission computerized tomography.

cortical atrophy is supported by hypometabolism on fluorodeoxyglucose (FDG) positron emission tomography (PET) in prefrontal and frontal,[53,54] temporal, and parietal regions in MSA-P,[54] and in frontal and inferior parietal regions in MSA-C.[55,56] Cortical thinning in cognitively impaired MSA patients has been reported in the same regions as in AD and PDD.[6]

A longitudinal volumetric MR study found a marked progression of brain atrophy in patients with MSA-P, including striatum, mesencephalon, thalamus, and cerebellum, but also cortical regions such as the primary sensorimotor cortex, supplementary motor area, lateral premotor cortex, medial frontal gyrus, middle frontal gyrus, orbitofrontal cortex, insula, posterior parietal cortex, and hippocampus.[9] Interestingly, short disease duration was correlated with progression of atrophy in the striatum, whereas longer disease duration was correlated with increasing atrophy in the cortical areas and cerebellar hemispheres, thus suggesting that early degeneration of the basal ganglia drives late-onset cortical atrophy.[9] Favoring this hypothesis of primary subcortical deafferentation of cortical regions, Paviour and colleagues[13] reported a correlation between pontine, midbrain, and cerebellar atrophy and impairment in different cognitive domains as well as global cognition in MSA patients,[13] which is supported by the observation of cerebellar hypoperfusion associated with visuospatial decline in MSA-C.[26] Conversely, prefrontal atrophy correlated with overall memory scores in MSA as a group,[20] and correlation between dorsolateral prefrontal hypoperfusion and visuospatial impairment in both motor MSA subtypes and executive dysfunction in MSA-P argue for primary cortical affection.[26] Decreased FDG uptake in the frontal lobes of early MSA-C, spreading to other cortical regions in advanced disease,[12] contrary to steady cerebellar hypometabolism, further supports the hypothesis of intrinsic cortical pathology in MSA.[55] Cholinergic denervation in MSA affecting all cerebral cortex regions highlights degeneration of all major cholinergic pathways important for attention, learning, and memory.[57]

In MSA patients, the mean cortical amyloid burden using Pittsburgh Compound B PET was comparable to that of controls.[6] However, the role of amyloid pathology should not be completely rejected, because substantial amyloid burden was reported in some demented MSA cases.[6]

Neuropathologic Considerations

Post-mortem studies have shown widespread subcortical degenerative changes in MSA brains. Both basal ganglia and cerebellar circuits are affected in MSA, and therefore the grading scale classifies predominant striatonigral (SND) and olivopontocerebellar (OPCA) type of degeneration.[58] Substantia nigra and putamen are mostly affected, and caudate nucleus and globus pallidus are also involved but to a lesser degree.[1,59] Cerebellar degeneration in MSA comprises severe loss of Purkinje cells and to lesser extent neurons in the dentate nucleus.[1]

With prominent nigral and putaminal degeneration[1] and secondary disruption of striato–pallido–thalamocortical circuits,[60] the concept of "subcortical dementia" may, at least partially, explain cognitive features of MSA. Despite the lack of detailed neuropsychological studies in patients with pathologically

proven MSA, the similarity of widespread subcortical pathology in other degenerative basal ganglia disorders indirectly suggests that the disruption of subcortico-cortical pathways is likely to mediate some of the cognitive disorders in MSA. Furthermore, executive, memory, visuospatial, and language impairment present within the group of patients with different types of cerebellar disorders indicate that the cerebellum participates in the organization of higher-order functions through its cortical inputs,[37] also favoring the concept of subcortical deafferentation.

Conversely, post-mortem evidence of frontal, temporal, and parietal cortical degeneration argue for additional primary cortical involvement in the cognitive deficits.[14,15,61-64] Neuronal loss, astrogliosis, and loss of myelinated fibers in deeper cortical layers of frontal lobes[14,15] and insula,[15] abundant GCIs found in deep cortical gray matter and white matter of frontal and parietal lobe,[14,15] vacuolation of glial cells in frontal cortex,[62] and ubiquitinated neuronal inclusions and dot-like structures in prefrontal areas[61] point toward prominent frontal degeneration in MSA. Temporal lobe atrophy with GCIs and neuronal cytoplasmic inclusions are confined to hippocampus, amygdala, insula, temporal, cingulate, and entorhinal regions of exceptionally long-term MSA cases.[63,64] Evidence for cortical degeneration in MSA recently led to the proposal of the term "cortical MSA" as a distinct clinicopathologic variant of MSA.[65] It has also been suggested that cases with severe temporal atrophy should be classified as a different subgroup.[66]

Degeneration of pedunculopontine tegmentum and dorsolateral tegmental nucleus[67,68] with abundant GCIs is in accordance with diminished cortical and subcortical acetylcholinesterase activity also observed in MSA based on PET results.[57,69]

Behavioral and Neuropsychiatric Symptoms in MSA

The influence of mood disturbances and anxiety on executive,[19,24] memory,[6,19] and visuospatial decline[6] is usually recognized as substantial in MSA, although not reported across all cohorts.[3] Approximately 40% to 85% of MSA patients report at least mild depression,[24,70-72] whereas one third are moderately to severely depressed.[70,71,73]

Anxiety is reported to affect 37% of MSA patients.[74] Although high levels of depression and anxiety are present in both MSA motor subtypes,[19,20,24,26,73] a dissociation has been reported, with MSA-P patients being more depressed and MSA-C subjects more anxious.[19,20]

Multiple system atrophy patients appear to suffer from apathy more frequently than PD patients,[44,75] with a mean rate of 65% in MSA.[44] Excessive daytime sleepiness affects more than 25% of MSA patients regardless of motor subtype, but contrary to PD it is unrelated to depression.[76,77]

Discussion and Outlook

In view of increasing awareness of cognitive impairments in PD and atypical parkinsonism, we aimed to emphasize the importance of paying more attention to cognitive and behavioral features in MSA. Based on existing evidence, we suggest that cognitive impairment is present in MSA more frequently than previously considered. Executive functions and fluency are the most commonly affected, whereas attention, memory, and visuospatial domains are sometimes impaired, and language mostly spared. Although visuospatial impairment may be one of the major difficulties in MSA-C patients,[26] MSA-P patients seem to exhibit more executive problems. In addition, MSA-P patients show more recall deficits improving with cueing, whereas learning disturbances appear more typically in MSA-C patients, suggesting that distinctive subcortical degeneration patterns (SND or OPCA) may differently influence cognition via cortical inputs in MSA. Generally, impaired attention and executive functions in both motor subtypes impact on all cognitive functions as well as behavioral features and severity of motor impairment. Both imaging and morphological data allow us to conclude that both deafferentation from subcortical structures and intrinsic cortical pathology play a role in cognitive decline, with the former being a feature of early disease, while the cortical contribution becomes apparent later in the disease course. However, among a considerable number of comparative studies, only one[3] provides neuropsychological data from a large number of MSA patients (Table 2). Furthermore, except for one small cohort of prospectively followed MSA patients,[38] evidence is mostly obtained from cross-sectional studies. A further shortcoming is the lack of a detailed assessment of cognitive functions in pathologically proven MSA cases.

Although the pattern of cognitive disturbances in MSA largely overlaps with cognitive impairment in other basal ganglia disorders, the quantitative difference may provide an important clue in clinically discriminating MSA from other synucleinopathies and PSP. Onset of clinically significant cognitive decline 5 to 6 years after disease onset or subtle problems even earlier, absence of hallucinations, prominent executive deficit, and gradual progression toward dementia in some cases contribute to the profile of cognitive decline in MSA patients. Hence, the MODIMSA neuropsychology group has launched efforts to examine the issue of cognitive impairment and dementia in MSA in greater detail, ultimately aiming to revise the current consensus criteria by including operational

guidelines for MSA dementia. The latter will serve to better recognize and characterize cognitively impaired MSA patients, a prerequisite for further research and therapeutic trials. ■

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Non-motor Symptoms of Parkinson's Disease

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Chapter 24

Visual function in Parkinson's disease

T. Baba, I. Estrada-Bellmann, E. Mori and A. Takeda

Introduction

Visual problems are common in Parkinson's disease (PD). A wide variety of visual symptoms have been described in PD, including blurred vision, diplopia, impaired colour vision, contrast insensitivity and visuospatial deficits [1]. Additionally, about a third of PD patients undergoing long-term dopaminergic treatment can present with visual hallucinations [2], although they may occur independently of dopaminergic medication. These symptoms affect the daily life of PD patients to varying degrees, and visual hallucinations in particular may be followed by cognitive decline and nursing home placement [3].

The neural basis of visual dysfunction in PD is not completely understood, but a combination of impairments in both bottom-up and top-down visual processing (i.e. the afferent flow of visual information and higher-order cognitive influences, respectively) may play a fundamental role [4–6]. Emerging evidence suggests that several levels of the visual pathway, from the retina to the primary visual cortex (the geniculostriate pathway), are preferentially affected in PD, causing impaired bottom-up visual processing [4]. Moreover, several functional imaging studies have reported alterations in top-down modulation of visual processing in PD, especially in association with visual hallucinations [7–9]. It seems to be plausible that many of the visual symptoms in PD can be explained by the interplay between these two mechanisms. This view may be somewhat oversimplified because it neglects the contribution of attentional deficits, brainstem dysregulation and the effects of administered drugs on visual function in PD [1,10,11]. However, such a systematic perspective will be helpful for a better understanding of the complexity of the visual symptoms in PD.

Overview of visual processing

It is generally thought that visual information is analysed at three levels—low, intermediate and high [12]. Particular sets of brain structures in the visual pathway are involved in each of these levels, with some overlap (Fig. 24.1).

Initially, elementary features of a visual scene, such as local contrast, orientation, colour and motion, are discriminated by low-level visual processing [13]. This first stage of visual processing starts at the retina [4]. The photoreceptor cells located in the outermost layer of the retina absorb light, and from there visual transduction starts. Then, retinal bipolar

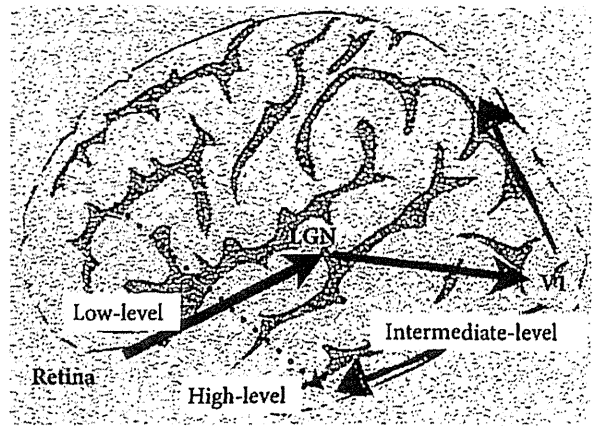

Fig. 24.1 Overview of visual processing. Visual information is analysed at three levels—low, intermediate and high. Solid lines suggest the bottom-up flow of visual information and the dotted line indicates the top-down modulation of visual information. Low-level visual information is processed in the geniculostriate pathway from the retina through the lateral geniculate nucleus (LGN) into the primary visual cortex. Low-level visual information is integrated into intermediate-level visual processing and delivered to the inferior temporal cortex, which is considered as the centre of high-level visual processing and the target of top-down modulation from various regions such as the prefrontal cortex and medial temporal lobe.

cells transfer the light signal to the retinal ganglion cells located in the inner retina. After leaving the retina, visual information is relayed via thalamic nuclei, including the lateral geniculate nucleus (LGN) and pulvinar, to the primary visual cortex (area V1). In this way, the retinal circuitry decomposes the retinal image into signals representing contrast, colour and movement.

Next, low-level visual information is assembled into contours and surfaces, and then those combined features are assigned to the representations of specific objects or background in intermediate-level visual processing. Many cortical areas are involved in these processes. Area V1 plays a role in contour integration and surface segmentation, in addition to the low-level perception of orientation and colour [13,14]. From area V1, visual information flows into the parietal lobe (dorsal stream) and the temporal lobe (ventral stream) [15]. The dorsal stream is involved in the analysis of movement and spatial localization. In contrast, the ventral stream, which contributes to object recognition, runs from areas V1 and V2 to area V4 and then into the high-level processing stage. In this way, elementary visual features are assembled into unified representations of objects and background, and the information is utilized as bottom-up signals in the next step.

Finally, object recognition is accomplished in high-level visual processing by the interplay between bottom-up inputs derived from the preceding stages and top-down signals converging from a variety of sources. The inferior temporal cortex plays a central role in high-level visual processing [16]. This area is known as the end stage of the ventral stream. Beyond the primary and secondary visual cortices, the ventral stream goes through the temporo-occipital (TPO) junction and culminates in the inferior temporal cortex [17,18].

In addition, it receives inputs from various cortical areas, including the prefrontal cortex and medial temporal lobe, and serves as a target of top-down modulation [18,19]. It is clinically well known that a lesion in the inferior temporal cortex causes impaired object recognition, known as visual agnosia [20]. Thus, the inferior temporal cortex, where bottom-up and top-down signals meet, is thought of as the primary centre for object recognition.

We will now discuss patterns of visual dysfunctions in PD, emphasizing their association with these visual processing stages.

Impairment in low-level visual processing in Parkinson's disease

As already mentioned, low-level visual processing starts at the retina and resolves the retinal image into minimal units of information concerned with contrast, colour and movement [4]. The retina comprises three layers of cell bodies and two interposed layers of fibres and synapses. It is known that dopaminergic cell bodies are located within the layer of amacrine cells at the border of the inner nuclear and inner plexiform layers. Dopamine exerts multiple effects on retinal cells, and helps to switch the active visual pathway from being rod-mediated to cone-mediated during periods of light—the process known as light adaptation [12].

Contrast sensitivity

In PD, marked dopaminergic deficiency is evident in the retina, in addition to the degeneration of nigrostriatal dopaminergic neurons [21,22]. Various visual impairments in PD are attributed to dopamine depletion within the retinal circuitry; one of the most well-known visual impairments is abnormal contrast sensitivity [23]. Contrast sensitivity is the visual ability to distinguish differences in luminance. Contrast sensitivity is predominantly regulated by the mechanisms of light adaptation, leading to perceptual constancy of contrast under varying conditions of illumination. Thus, dopamine depletion, either due to PD itself or during relatively unmedicated periods such as overnight, may cause altered light adaptation and result in contrast insensitivity, especially in the medium spectral frequencies at which human contrast perception is most sensitive [13]. Supporting this notion, the restoration of a normal spatial tuning function was noted upon the administration of levodopa [24,25]. Furthermore, it has been suggested that drug-induced parkinsonism exhibits deficits in contrast sensitivity in a pattern similar to that of PD [26]. Conversely, during levodopa-induced dyskinesias, a period of dopaminergic overstimulation, patients may experience pathologically increased inhibition of the 'surround' input for short periods of time, causing contrast sensitivity to fluctuate rapidly, leading to complaints of blurred vision [13,27].

Overall, dopamine is a vital neuromodulator for light adaptation. It seems likely that contrast insensitivity in PD may stem from the lack of retinal dopamine. However, orientation-specific loss of contrast sensitivity is observed in some PD patients which cannot be explained just by the retinal dysfunction, and the cortical influence on contrast insensitivity remains controversial [24,28].

Colour vision

Colour vision also begins in the retina [12]. In general, primates have three types of cone photoreceptors, distinguished on the basis of their wavelength preferences, specifically red, green and blue cones. Light stimuli absorbed in these photoreceptors are transformed into active potentials in the retinal bipolar cells and transmitted to the retinal ganglion cells. From the retinal ganglion cells, visual information is carried into the LGN and the primary visual cortex via segregated parallel visual pathways: parvocellular, magnocellular and koniocellular pathways. Among them, the parvocellular (red–green) and koniocellular (blue–yellow) pathways are involved in colour vision, whereas the magnocellular pathway has a major role in contrast vision. After the primary visual cortex, colour information is analysed as object surface information at subsequent processing stages.

Reduced colour vision is often an early feature of PD, and the most prominent deficits have been shown to be in the tritan (blue–yellow) axis [29,30]. Abnormality in the tritan axis in PD may be due to the simple fact that blue cones are more sparsely distributed in the retina and also lack surround inhibition, thus leaving the tritan axis particularly vulnerable. The Lanthony D-15 test and the Farnsworth–Munsell 100-hue test are the most widely used in the clinic for testing colour discrimination, but these tests have limited quantitative power. Thus, it may be somewhat difficult to detect impairments in colour vision in the early stages of PD, leading to inconsistent results [29,31]. Using more sophisticated colour discrimination tasks, a recent study suggested that the impairment in the tritan axis is due to normal ageing, and impaired protan (red–green)/deutan (luminance) axes are specific to PD [32]. It is also known that colour discrimination becomes worse with the progression of PD. Retinal dopaminergic deficiency may play a role in the colour discrimination deficits in PD, but many regions along the visual pathway participate in colour vision, and it is difficult to attribute impaired colour vision to retinal dysfunction alone. In addition, a recent study suggested that impaired colour vision is accompanied by a pre-motor parkinsonian state characterized by several non-motor symptoms including rapid eye movement sleep behaviour disorder [33].

Motion perception

Retinal ganglion cells and neurons in the LGN have concentric centre-surround receptive fields. These types of receptive fields are sensitive to moving objects. In low-level visual processing, information about an object's movement is transferred mainly by the magnocellular pathway. It has been thought that a dysfunction in the magnocellular pathway may cause a deficit in motion perception in PD, but a recent study described dorsal stream impairment as more important [34,35].

Impairment in intermediate-level visual processing in Parkinson's disease

In intermediate-level visual processing, low-level visual information is assembled into contours and surfaces through a hierarchy of cortical areas (Fig. 24.2 and Plate 5). It is

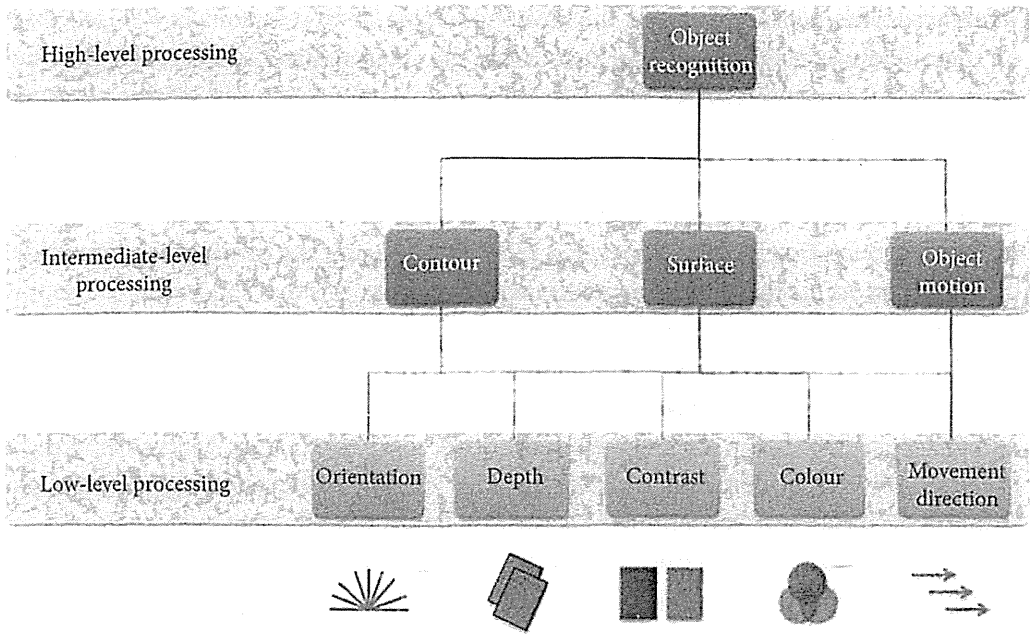

Fig. 24.2 The visual system is organized in both a hierarchical and a parallel manner. Low-level visual information is integrated at the intermediate-level processing stage. (See also Plate 5)

widely accepted that intermediate-level visual areas fall into two distinct streams, ventral and dorsal streams. The ventral stream is involved in object recognition, and the dorsal stream is engaged in the analysis of movement and spatial localization [12].

The following paragraphs describe how visual information is processed in each visual area (V1–V5) in the intermediate-level processing stage.

Area V1 is located on the surface of the occipital cortex, which receives inputs from the LGN and sends their projections into the ventral and dorsal streams. This area has orientation columns and blobs (clusters of colour-selective neurons). Orientation specificity, surface texture information and the integration of inputs from both eyes are developed in this area, leading to contour integration and surface segmentation.

Area V2 analyses information about an object's surface and depth (binocular disparity). It is also reported that this area responds to illusory contour stimuli. In addition, information from the magnocellular pathway enters the dorsal stream through areas V1 and V2. Area V4 is included in the ventral stream, and this area integrates information about colour and object shape, whereas area V5/MT is involved in the dorsal stream, integrates motion signals across space and is involved in the control of ocular movement.

There is evidence that intermediate-level visual processing is also impaired in PD. Imaging studies have demonstrated reduced metabolism and hypoperfusion in the occipital cortex as early characteristics of PD [36,37]. Furthermore, recent studies suggested that cortical cholinergic dysfunction occurs in the occipital cortex in early PD. The distribution of these radiographic abnormalities extends to higher-order visual areas along with disease progression in PD. Moreover, a pathological study demonstrated that the

visual association cortex is among the most vulnerable cortical regions in PD [38]. Based on these findings, it is little wonder that damage to intermediate-level visual areas causes various visual symptoms in PD. In fact, impairments in orientation and motion perception are frequently described. Furthermore, pre-attentive 'pop-out' of complex shapes, a phenomenon that is attributed to early visual cortical processing, is also impaired in PD [39].

There is insufficient evidence at present about impairments in contour integration and surface segmentation in PD. However, a recent study using the overlapping figure identification test seems to have provided an important clue. This test consists of overlapping line drawings of objects, for all of which the subjects are instructed to provide names (Fig. 24.3). In order to succeed at this task, it is necessary to detect the edges of objects and to correctly identify which edge belongs to which object. Thus proper contour integration and surface segmentation abilities are required to accomplish this test. Mori and colleagues [40] used this test for dementia with Lewy bodies (DLB), and reported significant impairments in DLB patients. Recently, the overlapping figure identification test was used for the assessment of PD, and the results suggested that ventral pathway dysfunction is associated with incorrect responses in this task [41], although the most prominent correlation was observed at the TPO junction (which participates in high-level visual processing).

Impairment in intermediate-level visual processing may lead to various visuoperceptual dysfunctions in PD, although we still do not have the full picture.

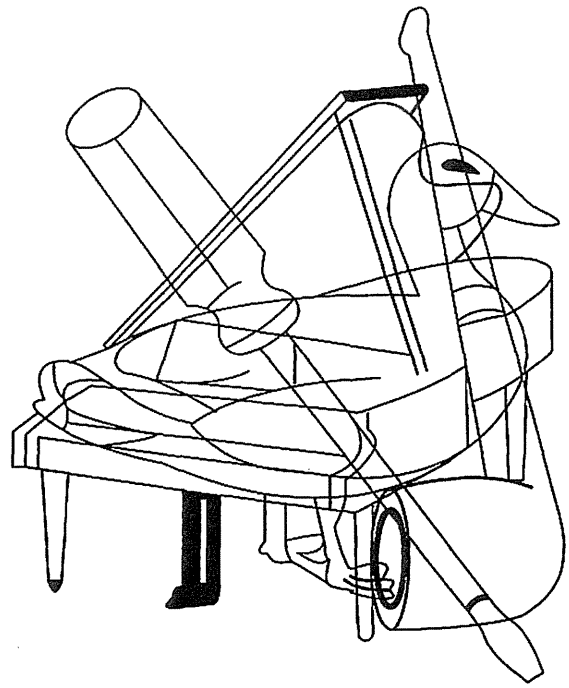

Fig. 24.3 The overlapping figure identification test. In this example, achromatic line drawings of a duck, a grand piano, a pipe and a flathead screwdriver overlap one another. Subjects are instructed to name all the objects.

Reproduced with permission from Ishioka T, Hirayama K, Hosokai Y, Takeda A, Suzuki K, Nishio Y, et al. Illusory misidentifications and cortical hypometabolism in Parkinson's disease. Mov Disord 2011; 26(5): 837–43.

Impairment in high-level visual processing in Parkinson's disease

Neurons in the inferior temporal cortex respond to complex visual stimuli, and dysfunction in this area causes impaired object recognition. A lesion in this area is known to cause impaired object recognition (visual agnosia) [20]. Indeed, impairments in object shape recognition were demonstrated in PD, and this finding may reflect a dysfunction in high-level visual processing. Impairment of high-level visual processing may also be involved in the pathogenesis of visual hallucinations in PD.

Visual hallucination occurs in about a third of PD patients during long-term dopaminergic therapy [11]. Visual hallucinations may also occur independently of dopaminergic therapy, based on reports from the pre-levodopa era, which suggests that dopaminergic medication is not the direct cause but seems to serve as a precipitating factor. In general, visual hallucinations are categorized into complex visual hallucinations and other minor hallucinations. Complex visual hallucinations have specific forms and are often animate, while other minor hallucinations include passage and presence hallucinations. These hallucinations affect activities of daily life in PD, and they are also known as a risk factor for nursing home placement and the development of dementia [3]. Thus, we need to understand the characteristics of these symptoms. Many factors are assumed to be involved in the pathogenesis of visual hallucinations in PD [10], such as dopaminergic overactivation, cholinergic deficits [42], retinal dysfunction, alteration in the sleep–wake cycle and impaired attention. However, an imbalance between bottom-up visual processing and top-down modulation may play an important role in the development of visual hallucinations in PD [5]. In the context of impairment of bottom-up visual processing, the occurrence of visual hallucinations has been thought of as a type of Charles Bonnet syndrome [43]. Furthermore, it has been shown that PD patients whose performance in the Lanthony D-15 colour test is one standard deviation below the mean have more than a four-fold increased risk of experiencing visual hallucinations [44]. In imaging studies, both hypoperfusion in the inferior temporal cortex and hyperperfusion/hypermetabolism in the frontal cortex were shown to be associated with visual hallucinations [7–9]. Pathological extension to the temporal lobe and amygdala was also reported to be associated with visual hallucinations in PD [45]. It has been suggested that visual hallucinations in PD might occur due to a dysregulation of gating and filtering of external perception and internal image production, but the pathogenesis of visual hallucinations in PD remains uncertain [43].

Despite its importance, there is no gold standard for testing and rating visual hallucinations in PD. The Unified Parkinson's Disease Rating Scale and the Neuropsychiatric Inventory have been used, but they have limitations in their detection sensitivity for visual hallucinations. Recently, the pareidolia test was invented as a tool to elicit visual hallucinations in the clinical setting [46], and the utility of this test for assessing visual hallucinations in DLB has been demonstrated (Fig. 24.4 and Plate 6). Considering the symptomatic similarities in the visual hallucinations of DLB and PD, it is expected that this test will also be useful for the evaluation of PD patients.

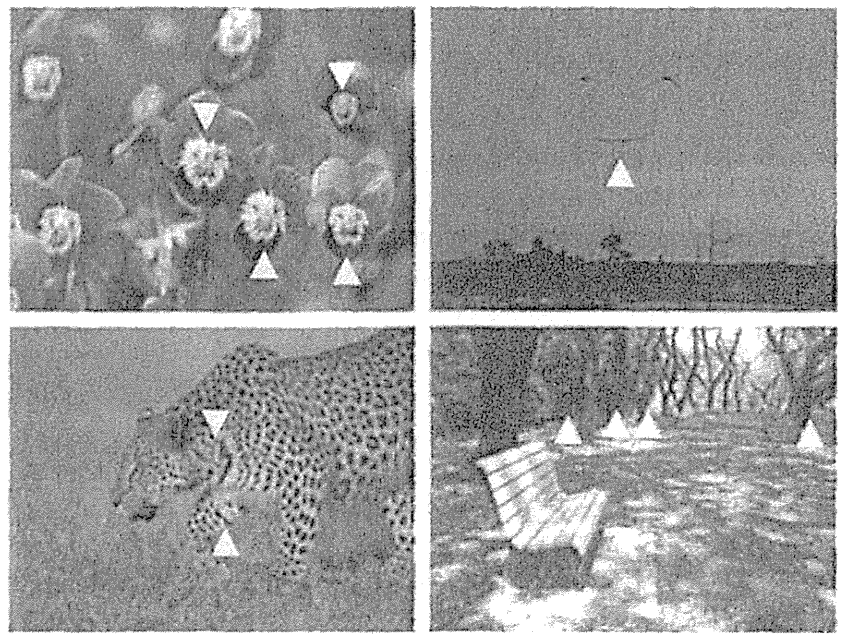

Fig. 24.4 Examples of the pareidolia test. Patients with dementia with Lewy bodies often misidentify objects or patterns in a picture as human faces (top left, top right and bottom left) or as people and animals (bottom right). (See also Plate 6)

Reproduced with permission from Uchiyama M, Nishio Y, Yokoi K, Hirayama K, Imamura T, Shimomura T, et al. Pareidolias: complex visual illusions in dementia with Lewy bodies. Brain: a Journal of Neurology 2012; 135(8): 2458–69.

Other visual symptoms in Parkinson's disease

Up to this point, we have discussed visual dysfunctions in PD and their relationship to the stages of visual processing. However, there are visual symptoms in PD patients that originate from outside the visual pathways, and these include abnormal ocular or eyelid movements (including diplopia). Ocular signs in PD are usually subtle, and studies have reported a high frequency of oculomotor signs and symptoms in PD patients with early, untreated disease, as well as those with moderate to late-stage PD. Deficits include disordered dynamic eye movements such as saccades and pursuit, convergence insufficiency, decreased blink rate, square wave jerks, blepharospasm, apraxia of eyelid opening and ocular micro-tremor [47].

Symptoms associated with oculomotor abnormalities include diplopia and difficulty reading, although the exact interplay between oculomotor abnormalities and the actual symptoms reported by patients has yet to be definitively elucidated.

Ocular movements

In PD, saccadic eye movements are often slow and hypometric, especially during vertical movements. The saccades most commonly affected are those conducted towards the remembered location of a previous visual target after its stimulus has been lost (so-called

remembered saccades) [47]. In addition to impaired saccadic movements, abnormalities in smooth pursuit eye movements are also impaired when following moving targets. The pursuit gain is reduced, and thus the eyes cannot keep up with the target, necessitating the aid of catch-up saccades to compensate. This results in a characteristic effect known as cogwheel pursuit, although despite the name, the underlying pathogenesis is different from cogwheel rigidity [48]. Fixation of the gaze on a specific visual target is often interrupted in PD via a phenomenon known as square wave jerks, which are back-to-back involuntary saccades of tiny amplitude that result in eye movement away from the fixed target and then rapidly back onto it again. Such movements are, however, not specific to PD alone and may occur in normal individuals. Following the administration of levodopa, an improvement is seen in saccadic accuracy and smooth pursuit gain, thus implicating dopamine or a downstream neurotransmitter system modulated by dopamine in controlling aspects of ocular movement.

Diplopia

Diplopia is a relatively common complaint in PD patients with normal visual acuity. One study described that more than a third of patients with PD reported symptoms consistent with diplopia. The recently reported NMSQuest study has suggested that diplopia may be under-reported and therefore an under-diagnosed problem in PD [49]. Bye and Chaudhuri [50], comparing a subset of 11 treated PD patients with and without symptomatic diplopia, reported that those with diplopia suffered a longer duration of PD (mean 9.5 years) than those without diplopia (mean 3.0 years). This suggests that diplopia may be more prevalent in PD sufferers with moderate-advanced stage disease than in patients with early-stage disease [47]. The mechanism of diplopia in PD is still unclear, although Bye and Chaudhuri [50] found that 64% of a diplopia group versus just 33% of a control group had demonstrable convergence insufficiency, supporting the previous study.

Nebe and Ebersach [51] reported a 'selective diplopia', in which double vision was limited to the duplication of single objects. All but one subject in this study reported that the double vision effect was extinguished when one eye was covered, thus indicating a binocular cause, correlating with the work of Bye and Chaudhuri. They also reported that more than half of the patients were suffering from current or previous visual hallucinations and three more patients developed hallucinations within 3 years of the onset of diplopia. These results raise the possibility that, in addition to distorted higher-level visual processing, selective diplopia is also related to the pathogenesis of visual hallucinations in PD. Furthermore, a link between dopaminergic medication and the onset of symptoms was reported in some cases.

Taken together, these studies on diplopia indicate a multifactorial aetiology, including subtle oculomotor abnormalities and convergence insufficiency, as well as a possible effect of medication.

Conclusions

A range of visual problems occurs in PD with varying frequency. Although the whole picture has not yet been elucidated, the underlying pathophysiology of visual dysfunction

in PD has become clearer with recent advances in neuroscience. Emerging evidence suggests that impairments in both bottom-up and top-down visual processing are related to the visual deficits in PD. Additionally, oculomotor abnormalities may also influence visual function in PD. Further study is needed to untangle the complexity of visual symptoms in PD.

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◆ Human Brain Mapping 35:1896–1905 (2014) ◆

Bidirectional Effects on Interhemispheric Resting-State Functional Connectivity Induced by Excitatory and Inhibitory Repetitive Transcranial Magnetic Stimulation

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Abstract: Several recent studies using functional magnetic resonance imaging (fMRI) have shown that repetitive transcranial magnetic stimulation (rTMS) affects not only brain activity in stimulated regions but also resting-state functional connectivity (RSFC) between the stimulated region and other remote regions. However, these studies have only demonstrated an effect of either excitatory or inhibitory rTMS on RSFC, and have not clearly shown the bidirectional effects of both types of rTMS. Here, we addressed this issue by performing excitatory and inhibitory quadripulse TMS (QPS), which is considered to exert relatively large and long-lasting effects on cortical excitability. We found that excitatory rTMS (QPS with interstimulus intervals of 5 ms) decreased interhemispheric RSFC between bilateral primary motor cortices, whereas inhibitory rTMS (QPS with interstimulus intervals of 50 ms) increased interhemispheric RSFC. The magnitude of these effects on RSFC was significantly correlated with that

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of rTMS-induced effects on motor evoked potential from the corresponding muscle. The bidirectional effects of QPS were also observed in the stimulation over prefrontal and parietal association areas. These findings provide evidence for the robust bidirectional effects of excitatory and inhibitory rTMSs on RSFC, and raise a possibility that QPS can be a powerful tool to modulate RSFC. *Hum Brain Mapp 35:1896–1905, 2014.*

Key words: fMRI; rs-fcMRI; rTMS; QPS; transcallosal connection

INTRODUCTION

Transcranial magnetic stimulation (TMS) is one of the noninvasive tools to stimulate neurons in the human brain [Allen et al., 2007; Barker et al., 1985; Merton and Morton, 1980], and has recently been used for treating neurological or neuropsychiatric diseases such as Parkinson disease and severe depression [George et al., 1999; Post et al., 1999; Pridmore and Belmaker, 1999]. For experimental purposes, repetitive TMS (rTMS) has been applied as one of the valuable tools to induce reversible changes in an intact human brain [Fox et al., 2012; Pascual-Leone et al., 2000]. rTMS has also been used to show the causal relationship between certain types of behavior and brain activity or structures [Fox et al., 2012; Kanai et al., 2011; O'Shea et al., 2007; Romei et al., 2011; Strafella et al., 2001; van Schouwenburg et al., 2012; Zaretskaya et al., 2010].

Recently, several studies [Eldaief et al., 2011; van der Werf et al., 2010; Vercammen et al., 2010] have taken advantage of functional magnetic resonance imaging (fMRI) to investigate effects of rTMS on resting-state functional connectivity (RSFC) [Beckmann et al., 2005; Biswal et al., 1995, 2010; Damoiseaux et al., 2006; Duann et al., 2009; Fox and Raichle, 2007; Fox et al., 2005; Greicius et al., 2003; Honey et al., 2007; Kilpatrick et al., 2006; Koyama et al., 2011; Murphy et al., 2009; Smith et al., 2009; Tian et al., 2012; Toro et al., 2008; van Kesteren et al., 2010; Vincent et al., 2006]. However, all the previous studies have mainly reported an effect induced by either excitatory or inhibitory rTMS: Some of the studies have shown significant effects induced by inhibitory rTMS on RSFC [van der Werf et al., 2010; Vercammen et al., 2010]. Another study has shown the effects of both excitatory and inhibitory rTMSs, but the influence induced by inhibitory rTMS was found to be limited and moderate compared with that induced by excitatory rTMS [Eldaief et al., 2011]. Consequently, despite the importance of establishing a protocol to clearly modulate functional connectivity for clinical and experimental purposes, to the best of our knowledge, effects of the excitatory and inhibitory rTMSs of similar magnitudes on RSFC have not been reported.

In particular, the bidirectional modulation of functional connectivity should be requisite for clinical purposes because some neurological and psychiatric disorders induce an increase or a decrease in functional connectivity [Fox et al., 2012]. For example, brain strokes in the motor area pathologically enhance transcallosal inhibition from the intact motor area over the lesion motor area, which is considered to prevent the recovery of functions of the lesion area [Duque et al., 2005; Grefkes et al., 2008; Murase et al., 2004]. Moreover, patients with schizophrenia have been shown to have pathologically reduced interhemispheric prefrontal functional connectivity [Meyer-Lindenberg, 2010; Meyer-Lindenberg et al., 2005] and an abnormal increase in functional connectivity with the medial temporal regions [Meyer-Lindenberg, 2010; Whitfield-Gabrieli et al., 2009]. A protocol of rTMS that enables bidirectional modulation of functional connectivity could be one of the promising tools to improve these neurological and psychiatric symptoms.

In the present study, we aimed to address this issue by investigating the effects of quadripulse rTMS (QPS) on interhemispheric RSFC between contralateral brain regions. The rTMS protocol (Fig. 1A) is reported to attain long-lasting effect for ~30 min to 2 h after the stimulation [Hamada et al., 2007, 2008], which is much longer than that induced by conventional rTMS (ca. 15 min). In addition, to improve the sensitivity to the rTMS-induced effects, we mainly measured the changes in interhemispheric RSFC between bilateral homologous regions. According to previous studies [Stark et al., 2008; Zuo et al., 2010], the interhemispheric RSFC consistently shows a large value, which implies that the effects on interhemispheric RSFC are robust to various noises such as individual differences and fluctuations of rTMS stimulation. By administering QPS over inter-hemispheric RSFC, we aimed at demonstrating the bidirectional effects of excitatory and inhibitory rTMS on RSFC.

METHODS

Subjects

Six healthy adult male volunteers (27- to 43-years old) participated in the present experiments after providing their written informed consent. None of the subjects had any neurological, psychiatric, or other medical problems, or had any contraindication to TMS [Wassermann, 1998]. The procedure of rTMS was in compliance with the

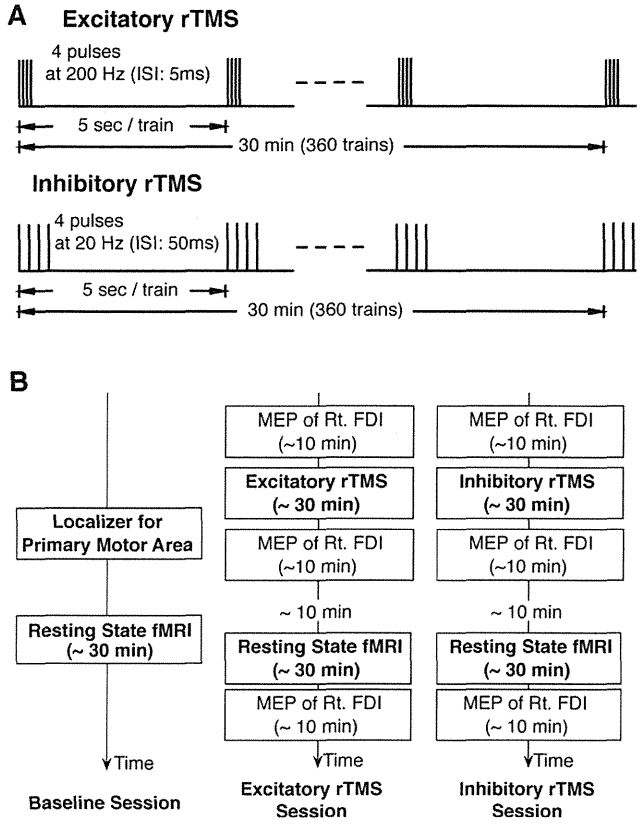

Figure 1.

Experimental procedure. **A.** rTMS Protocol. Two types of rTMS were used in the present study. The protocol for excitatory rTMS consisted of 360 trains of quadripulse rTMS at 5-ms interstimulus interval (ISI), whereas that for inhibitory rTMS consisted of 360 trains of quadripulse rTMS at 50 ms ISI. **B.** Experimental Design. The present overall experimental design consisted of three sessions: the baseline, excitatory and inhibitory rTMS sessions. In the baseline session, the subjects underwent a localizer fMRI scan and a resting-state fMRI scan. In the two types of rTMS, the subjects were administrated by rTMS ~10 min before resting-state fMRI scan. The order of the two rTMS sessions was counter-balanced across subjects, and the sessions were conducted at an interval longer than 1 week.

guidelines for experimentation on humans [Drummond, 2009]. The entire procedures of both fMRI and rTMS were approved by the Institutional Review Board of School of Medicine, The University of Tokyo.

Overall Design

We calculated RSFC from MRI data obtained before and after one of two types of rTMS (excitatory and inhibitory rTMS) (Fig. 1A) over the left primary motor area (M1). The experiment consisted of three sessions: the baseline, excitatory rTMS, and inhibitory rTMS sessions (Fig. 1B). In the baseline session, the participants were first subjected to functional localizer scanning to identify the left M1 for the right first dorsal interosseous muscle (FDI) individually, and then underwent RSFC scanning as the control. Excitatory and inhibitory rTMSs were applied with an interval of at least 1 week, and the order of these two sessions was randomized and counterbalanced across subjects. Before the rTMS session, motor evoked potentials (MEPs) were recorded from the right FDI as a control. Thereafter, either type of rTMS was applied over the left M1 for 30 min. Approximately 10 min after the rTMS session, we conducted resting-state fMRI for ~30 min. After fMRI, MEPs were recorded from the right FDI again to confirm the after-effects.

MEP Measurement Procedures

The MEP measurement procedure was essentially the same as that in our previous studies [Hamada et al., 2007, 2008]. MEPs were recorded from the right first FDI muscle using pairs of Ag/AgCl surface cup electrodes (9-mm diameter) placed over the muscle belly (active) and the metacarpophalangeal joint of the index finger (reference). The signals were input to an amplifier (Biotop; GE Marquette Medical Systems, Japan) through filters set at 100 Hz and 3 kHz, and were digitized and stored on a computer for later offline analyses (TMS BiStim tester; Medical Try System, Japan). TMS was administered using a handheld figure-of-eight coil (9-cm external diameter at each wing; The Magstim, Whitland, Dyfed, UK). QPS, i.e., a train of four monophasic magnetic pulses, delivered using four magnetic stimulators (Magstim 2002; The Magstim) connected to a specially designed combining module (The Magstim).

Before rTMS, we conducted single-pulse TMS experiments to determine the following two parameters. First, the optimal stimulation site for the right FDI muscle was determined in each subject as the site eliciting the largest MEP [Hamada et al., 2007, 2008]. Second, the active motor threshold (AMT) for the FDI muscle was defined as the lowest intensity that evoked a small response (>100 μV) when the subjects maintained a slight contraction of the right FDI (~10% of the maximum voluntary contraction) in more than 5 of 10 consecutive trials. MEPs were also recorded for monitoring M1 excitability changes after rTMS. About 10 min after the end of fMRI, we recorded 20 consecutive MEPs from FDI to compare them with the control MEPs recorded before rTMS.

rTMS Procedure

The rTMS procedure was the same as that in our previous studies [Hamada et al., 2007, 2008]. QPS consisted of trains of four TMS pulses with an inter-train interval (ITI) of 5 s (Fig. 1A). The target region was the same as the left M1 that was determined by MEP measurement. Each train