Comparative Neuropsychology of Cortical and Subcortical Dementia

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ABSTRACT: The terms "cortical" and "subcortical" dementia are controversial; however, the clinical distinction between them is real. For example, although Alzheimer's and Parkinson's disease (prototypical of cortical and subcortical dementia, respectively) share clinical features, they differ in the presence of aphasia, apraxia, and agnosia in Alzheimer's disease but not in Parkinson's dementia. We review our studies aimed at clarifying the mechanisms underlying the differences between these neurological disorders. Experimental paradigms adopted from animal models were used to study the functional anatomy and neuropsychological characteristics of Alzheimer's and Parkinson's disease. The tasks administered include delayed alternation (DA) and delayed response (DR), which are sensitive to frontal system damage, and tactile discrimination learning (TOL) and reversal (TRL) paradigms sensitive to parietal system damage. Alzheimer's patients were significantly impaired on all tasks whereas Parkinsonians with dementia were impaired only on DR and TRL. Consideration of neuroanatomical and neuropsychological mechanisms involved in DA, DR, TOL, and TRL appears to have sharpened the distinction between Alzheimer's and Parkinson's dementia. Dementia in Alzheimer's disease may involve dorsolateral frontal, orbitofrontal and parietal systems. In contrast, dementia in Parkinson's disease may involve prominent dorsolateral frontal system damage.

RÉSUMÉ: Neuropsychologie comparative des démences corticales et sous-corticales. Les termes démence "corticale" et "sous-corticale" sont des termes controversés; cependant, la distinction clinique entre les entité qu'ils désignent est réelle. Même si la maladie d'Alzheimer et la maladie de Parkinson par exemple (respectivement prototypes de la démence corticale et sous-corticale), ont des manifestations cliniques communes, elles diffèrent par la présence d'aphasie, d'apraxie et d'agnosie dans la maladie d'Alzheimer et leur absence dans la démence du Parkinson. Nous revoyons nos études visant à clarifier les mécanismes sous-jacents aux différences entre ces entités neurologiques. Nous avons utilisé des paradigmes expérimentaux adaptés des modèles animaux pour étudier l'anatomophysiologie et les caractéristiques neuropsychologiques de la maladie d'Alzheimer et de la maladie de Parkinson. Parmi les épreuves administrées citons: l'alterance différée (AD) et la réponse différée (RD) qui sont des épreuves très sensibles à l'atteinte du système frontal; l'apprentissage de la discrimination tactile (ADT) et l'apprentissage de l'inversion tactile (AIT) qui sont des paradigmes sensibles à l'atteinte du système pariétal. Toutes les épreuves étaient significativement anormales chez les patients souffrant de la maladie d'Alzheimer, alors que seulement les épreuves de la RD et de l'AIT étaient altérées chez les parkinsoniens. L'étude des mécanismes neuro-anatomiques et neuropsychologiques impliqués dans l'AD, la RD, l'ADT et l'AIT semble avoir précisé la distinction entre la démence de la maladie d'Alzheimer et celle de la maladie de Parkinson.

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Although non-human animal models have long supported a role for focal cortical and subcortical brain structures in a variety of cognitive functions[1-3] it is only recently that parallel concepts have emerged linking circumscribed pathology to intellectual deficits in humans with neurological disease.[4-6] The anatomical and physiological mechanisms underlying these intellectual deficits, however, are poorly understood. "Subcortical dementia", the term originally applied to the constellation of human cognitive deficits attributed to subcortical brain damage is characterized by 1) memory loss; 2) impaired manipulation of acquired knowledge (i.e. calculating and abstracting ability); 3) personality changes marked by apathy and inertia; and 4) general slowness of thought processes.[4] In contrast to subcortical dementia is the concept of "cortical dementia" which refers to the pattern of cognitive deficits attributed to pathology in the cerebral cortex.[4,5] The cortical dementias share many features with subcortical dementia, but are distinguished from subcortical dementia by the presence of aphasia, apraxia and agnosia.[7]

Although useful *clinical* concepts,[7,8,9] subcortical and cortical dementia have been challenged as valid *anatomical* entities

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on the basis of neuropathological data. Reports have shown that cortical lesions may be important in the pathogenesis of subcortical dementia and that subcortical lesions may be significant in cortical dementia. For example, in Alzheimer's disease, the prototype of cortical dementia, there is a loss of cholinergic neurons in the nucleus basalis of Meynert,[10] a subcortical structure in the basal forebrain. This nucleus is the major source of cholinergic innervation to the cerebral cortex.[11-14] The clearly demonstrated involvement of the cholinergic system in memory[15-20] supports the concept that the nucleus basalis of Meynert is important for cognitive function. Likewise, Parkinson's and Huntington's disease, the two most thoroughly studied neurological disorders characterized by the classical behavioural pattern of subcortical dementia, both involve damage in cortical regions. Neurofibrillary tangles and senile plaques have been well-documented in the cerebral cortex in Parkinson's disease,[21-23] and cortical cell loss and gliosis are seen in Huntington's disease.[24]

The major issue surrounding the controversy about the validity of subcortical and cortical dementias as distinct clinical entities has been therefore, the nature of the underlying neuropathology rather than the neuropsychological mechanisms underlying these two forms of cognitive impairment. Since traditional behavioural experimental approaches have not been successful in resolving this issue, we employed a different strategy involving a direct application of experimental paradigms adopted from the animal literature to the study of neurobehavioural patterns of human cortical and subcortical dementia. Termed comparative neuropsychology,[25-27] the approach is based upon techniques that have a long history of proven reliability and validity in demonstrating brain-behaviour relationships in non-human primates. Within the last five years these same techniques have clearly established themselves as valuable tools for identifying cognitive impairment in brain damaged humans.[26,28-32] The use of animal models to study humans with dementia, therefore, not only draws upon a rich and extensive literature, but also allows for greatly needed direct comparisons of behavioural deficits observed in humans and animals with damage of homologous brain structures. Aspects of our use of the comparative neuropsychology approach[33,34] to study cortical and subcortical dementia will be the subject of this review. We selected Alzheimer's disease as the model for cortical dementia and Parkinson's disease as the model for subcortical dementia. When making our comparisons we were careful to equate the groups for severity of dementia.

We employed experimental paradigms which have been validated for the demonstration of deficits linked to damage in two different brain systems implicated in Alzheimer's and Parkinson's disease: 1) the prefrontal cortical/subcortical system, and 2) the parietal cortical/subcortical system. The tasks associated with frontal system functions consisted of delayed alternation (DA) and delayed response (DR).[28,31,35] All of our tasks will be described later, but it should be noted that different aspects of each of them are mediated by separate cortical/subcortical neuronal networks.[2,36-40] For assessment of parietal system functions we used tactile discrimination learning (TOL) and reversal (TRL) paradigms. TOL is sensitive to bilateral parietal lobe lesions in non-human primates,[40] and TRL provides a measure or perseveration with touch as in the input modality.

Although both Alzheimer's and Parkinson's patients with dementia were expected to demonstrate behavioural changes consistent with frontal lobe damage, we hypothesized that the nature of the impairment would be different and that this would be reflected by distinct performance profiles on the DA and DR tasks. We also predicted that the patients with Alzheimer's and Parkinson's dementia would show different performance profiles on the tactile learning paradigm (the measure of parietal lobe function) based on clinical, neuropathological[41] and positron emission tomography (PET) scanning[42,43] data which suggest that parietal lobe impairments are prominent in Alzheimer's disease. In contrast, the dementia of Parkinson's disease is characterized by prominent frontal lobe deficits.[9] We, therefore, hypothesized that the profiles of the subjects studied using paradigms adopted from animal models would serve to differentiate Alzheimer's from Parkinson's dementia at a behavioural level and that the performance profile would also provide insights into the anatomical mechanisms underlying the behavioural deficits.

Methods

We compared the performance of patients with idiopathic Parkinson's disease and dementia (n = 15) with that of patients with Alzheimer's disease (n = 14), Parkinson's disease without dementia (n = 13) and normal controls (n = 22). All 64 subjects participated on the DA and DR tasks. However, 3 patients with Alzheimer's disease and 2 with Parkinson's disease and dementia did not participate in the tactile learning experiments. The Parkinsons' patients were separated into demented and non-demented groups on the basis of their performance on the Mattis Dementia Rating Scale.[44] The criterion for dementia was determined on the basis of normative data obtained from the 22 normal controls. Parkinson's patients with scores falling below the range of scores attained by any of the normal controls (133-144) were classified as having dementia. The patients with Alzheimer's disease were equated for severity of dementia to the patients with Parkinson's disease and dementia, using the Dementia Rating Scale. Detailed patient descriptions can be found elsewhere.[33,34]

The methodology for DA and DR tasks has been described in detail.[33] The apparatus and stimuli were the same in both tasks but the experimental procedures differed. Briefly, on DA, subjects were required to find a penny in one of two reinforcement wells by learning that the location of the penny was being alternated by the experimenter from side to side after each correct response. The reinforcement wells were each covered by an identical black lid and were placed 23.5 cm apart in a wooden frame. There was a 5 second inter-trial interval. Testing continued until subjects discovered that the penny was being alternated from side to side to a learning criterion of 12 consecutive correct responses or until a failure criterion of 50 trials (i.e. they did not solve the problem after 50 trials).

On DR, subjects were required to retrieve the penny following a delay of 0, 10, 30 or 60 seconds, respectively, after seeing it being placed, according to a modified random sequence,[45] under one of the two black lids. During the delay period the covered wells were hidden from view by a curtain. Learning criterion was 9 correct responses in a block of 10 trials on each delay condition and failure criterion was 40 trials on each delay condition.

For the tactile learning experiment[34] there were two components, TOL and TRL. On TOL subjects were required to find a

penny under one of two wells covered by a lid, as before. However, the lids were hidden from view by a curtain and the subjects had to identify the correct lid using tactile information obtained by palpating a raised pattern on its surface (X vs O). One of the two patterns was considered "correct" and always had the penny underneath it. The patterned lids appeared in the left and right positions according to a modified random schedule.[45] Subjects continued until they made 9 correct responses in a block of 10 trials or until a failure criterion of 200 trials. After subjects completed the TOL task, TRL began. The pattern that was not reinforced initially became the reinforced stimulus (i.e. correct stimulus) and subjects had to reverse what they originally learned and find the penny under the other lid. Learning criterion again was 9 correct trials in a block of 10 trials, and failure criterion was 50 trials. After the subject completed this first reversal problem there followed 3 other successive reversal problems, each with the same learning and failure criteria.

Results

Detailed results have been reported[33,34] elsewhere and will only be summarized here (Table 1). The Parkinson's patients with dementia had significant deficits on DR but not on DA, whereas the Alzheimer patients were impaired on both tasks. TOL was significantly more impaired in the Alzheimer's compared to the demented Parkinson's patients. Both Alzheimer's and demented Parkinson's patients were impaired on TRL but the Alzheimer patients showed significantly more perseverative type errors than did the Parkinson's patients.

The observed deficits cannot be attributed to group differences in age or education since these variables were included as co-variates in the regression analyses used to analyze the data.

Table 1: Performance Profile of Subject Groups on Experimental Tasks

			Tactile Learning	
	Delayed Alternation	Delayed Response	Original Learning	Reversal Learning
Alzheimer's Disease	+	+	+	+
Parkinson's Disease with Dementia	−	+	−	+
Parkinson's Disease without Dementia	−	−	−	−
Normal Controls	−	−	−	−

+ deficit
− no deficit

Discussion

In Alzheimer's and Parkinson's disease with dementia we found distinct performance profiles on DA, DR and tactile discrimination learning even though both groups had been equated for severity of dementia. In Alzheimer's disease DA, DR, TOL and TRL were all significantly impaired whereas in Parkinson's disease with dementia there were significant deficits only on DR and TRL.

Although deficits on DR occur after lesions within both the dorsolateral frontal system and orbitofrontal system, they are more prominent following dorsolateral frontal damage.[46,47] Mild deficits on DR can also be produced by lesions in the head of the caudate[1] and dorsomedial nucleus of the thalamus.[48,49] The head of the caudate receives direct projections from dorsolateral frontal cortex.[50] The dorsomedial nucleus of the thalamus is also a well documented frontal projection site.[51,52] Both subcortical structures are therefore part of the frontal projection system. Our findings on DR suggest that dorsolateral frontal cortex, or its related projection systems, are involved in the pathophysiology of the dementia in both Alzheimer's and Parkinson's disease. Since the head of the caudate nucleus is an integral component of the nigrostriatal system that is involved in Parkinson's disease,[53] it is reasonable to raise the question whether the critical lesion for the DR deficits in Parkinson's disease is in the head of the caudate rather than the prefrontal cortex or other frontal projection sites. In fact, the lesion may even be in the anterodorsal sector of the head of the caudate since this is the area to which dorsolateral frontal cortex primarily projects.[50] It is noteworthy that, within the caudate nucleus in Parkinson's patients, it is the anterior portion of the caudate head which undergoes the most severe loss of dopamine concentration.[54] Additional studies however, are needed to address this issue further.

Performance on DA is sensitive to lesions in the dorsolateral and orbitofrontal cortex,[35] head of the caudate,[1,2] hippocampus,[55] amygdala,[55] temporal cortex,[56] dorsomedial nucleus of the thalamus[48,49] and hypothalamus.[3] Poor performance on DA has been related to abnormal perseverative responding. Since orbitofrontal lesions produce the most prominent deficits in perseveration,[57] orbitofrontal system damage may be important in explaining the deficit on DA in Alzheimer's disease. Alternatively, the DA deficit in Alzheimer's disease may be related to one of the other multiple lesion sites implicated in DA deficits.

The finding that tactile learning of a new problem (TOL) was significantly impaired in patients with Alzheimer's disease compared to patients with idiopathic Parkinson's disease and dementia also supports the concept that there are selective differences between the patterns of impairment characterizing the dementias of Alzheimer's and Parkinson's disease. Comparative data from non-human animal models suggest that deficits in TOL are sensitive to lesions in the parietal lobes.[40] Clinical data, as well as recent PET studies,[42,43] and neuropathological data[41] all suggest that parietal lobe involvement is prominent and appears early in the progression of Alzheimer's disease. In our studies,[33,34] whereas only the Alzheimer patients were impaired in learning the original tactile discrimination (TOL), both the Alzheimer's and the demented Parkinson's groups were significantly impaired in their ability to use the reversal strategy. However, an analysis of error patterns of the two groups showed that there was a difference in the types of errors that they made. As expected, perseverative responding was a significantly greater factor in the deficits seen in the Alzheimer patients compared to all other groups; that is, they continued to choose the previously rewarded pattern despite a shift in reinforcement to the other stimulus. Since perseveration is associated with frontal lobe lesions,[58] the perseverative tendency in the Alzheimer patients is likely due to the known frontal pathology in this disorder.[58] The abnormal perseverative behaviour on the tactile task also supports the findings suggestive of frontal system deficits already reported in Alzheimer's dementia using DA and DR.

Conclusion

There is an increasing literature suggesting that there are separate mechanisms underlying the dementias of Alzheimer's

and Parkinson's disease.[60-62] The results of the studies reviewed here lend strong support to this notion. Although the labels "subcortical" and "cortical" for the cognitive deficits in Parkinson's and Alzheimer's disease may not be accurate from an anatomical point of view, the growing body of data suggests that the concept underlying these labels, i.e. that they represent distinct patterns of dementia, remains viable.

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