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COMPARISON OF QUALITATIVE AND QUANTITATIVE CLOCK DRAWING SCORES AMONG PARKINSON'S AND ALZHEIMER'S DISEASE PATIENTS

by

Lisa Daberkow Stalp

A DISSERTATION

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DISSERTATION TITLE

Comparison of Qualitative and Quantitative Clock Drawing Scores Among Parkinson's and Alzheimer's Disease Patients

BY

Lisa J. Daberkow-Stalp

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GRADUATE COLLEGE
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COMPARISON OF QUALITATIVE AND QUANTITATIVE CLOCK DRAWING SCORES AMONG PARKINSON'S AND ALZHEIMER'S DISEASE PATIENTS

Lisa Daberkow Stalp, Ph.D.

University of Nebraska, 1996

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This study addresses part of the theoretical, functional distinction between "cortical" and "subcortical" dementia, namely, whether or not a progressive disease impacting primarily subcortical regions of the brain (Parkinson's disease - PD) will result in relatively greater graphomotor behavioral deficits, while a progressive disease impacting primarily cortical regions (Alzheimer's disease - AD) will result in relatively greater conceptual deficits in cognitive functioning. A clinical instrument which prior research suggests may be useful in identifying these deficits in demented patients, the Clock Drawing Test, was administered according to the method developed by Rouleau et al. (1992). One hundred eleven subjects participated, including elderly controls (NC), AD patients, PD patients with dementia (DPD), and PD patients without dementia (NDPD). Dementia groups were matched for severity of impairment. In two analyses using command, copy, and command-copy change conditions, total scores tended to differentiate the AD group from normal controls consistently but these scores were less consistent for the DPD group. Generally, the DPD group did not differ from the NDPD group, although like the AD group, these scores

did tend to differentiate DPD subjects from normal controls. Qualitative error scores for these conditions did not consistently support the predicted relationship, although predicted differences were commonly in the expected direction. To access clinical utility of the Clock Drawing Test, an actuarial analysis of individual scores of dementia was undertaken. Hit rates based on Clock Test scores were above chance but not sufficient in avoiding misses (sensitivity) in diagnosis to warrant the use of this measure alone to assess dementia. However, the Clock Drawing Test appears to be useful when used with other clinical measures that seek convergent validity. Finally, this research does not demonstrate pervasive evidence of a distinction between the functional characteristics of cortical and subcortical dementia. The cortical/subcortical classification, when applied to cognitive and behavioral consequences of progressive diseases of the brain, may not be sufficient to describe the complex relationship between dementias of various etiologies.

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Introduction

Dementia is a syndrome of acquired brain dysfunction with persistent deficits in multiple neuropsychological domains (Cummings & Benson, 1988). Alzheimer's disease is the most common etiology of dementia accounting for at least 50% of the moderate to severe cases (Brown & Marsden, 1988). Other diseases that have dementia as a significant feature include Huntington's disease, Parkinson's disease, Pick's disease, and progressive supranuclear palsy.

Although dementia was historically viewed as a unitary disorder of intellectual loss, more recent studies have indicated that etiologically different types of dementia have unique qualitative and quantitative patterns of neuropsychological impairment (Butters, Salmon, & Heindel, 1990; Stern, Richards, Sano, & Mayeux, 1993; Huber, Shuttleworth, & Freidenberg, 1989). Based on these clinical differences, one classification of dementia distinguishes between cortical and subcortical dementia.

Cortical and Subcortical Dementia

Within the cortical/subcortical classification, each group is assumed to share a common pattern of intellectual deficits and exhibit dysfunction primarily in either the cortical or subcortical structures of the brain. This classification is also based on the theoretical assumption that there are qualitative and quantitative clinical or functional differences between the cortical and subcortical

dementias (Albert, 1978; Benson, 1983; Cummings & Benson, 1984; McHugh & Folstein, 1975; Huber & Paulson, 1985).

According to the theory, both types of dementia exhibit disturbances in the areas of memory, visuo-spatial skills, and intelligence, but these impairments are more severe in the cortical dementias. In addition, the cortical dementias, including Alzheimer's disease, are characterized by hallmark signs of aphasia, agnosia, apraxia, acalculia, and amnesia, which are not found in subcortical dementias. Cummings (1986) conceptualizes these hallmarks as impairments of instrumental functions (language, praxis, perceptual recognition, memory, and calculation), which are dependent on intact focal areas of the cerebral cortex and neuronal connections between these areas. Therefore, neuropathology in this class of dementia is thought to primarily involve cortical brain structures (Cummings & Benson, 1983; Benson, 1983).

In contrast, the subcortical dementias are thought to show greater impairment in the form of executive deficits (cognitive slowing, difficulty developing problem-solving strategies, shifting ideas, abstracting, and manipulating acquired knowledge), personality and affective changes, including depression and apathy. They also show impairments of the fundamental functions of arousal and attention (Cummings, 1986; Albert, 1974; McHugh & Folstein, 1975; Cummings, 1983; Cummings & Benson, 1984). The

neuropathology of the subcortical dementias is located predominantly in deep, gray matter structures including the thalamus, basal ganglia, and related brain-stem nuclei. The subcortical nuclei connect widely with the cerebral cortex and have major connections with the frontal lobe and the limbic system. These brain structures are less discretely organized than the neuroanatomy implicated in cortical dementia (Albert, 1974; McHugh & Folstein, 1975; Cummings & Benson, 1983; Cummings & Benson, 1984).

The term subcortical dementia was first applied to degenerative diseases including progressive supranuclear palsy, Huntington's, and Parkinson's disease (Albert, Feldman, & Willis, 1974; McHugh & Folstein, 1975), and has been extended to include infarctions (Cummings & Benson, 1983; Guberman & Stuss, 1983) and metabolic disorders (Bachman & Albert, 1984) that primarily affect the subcortical gray matter and show similar neuropsychological symptoms.

The validity of the cortical/subcortical distinction has been debated in the literature. In a number of literature reviews, Cummings and Benson (Cummings & Benson, 1984; Cummings, 1988) state that there is evidence to support this distinction as a useful clinical and valid theoretical concept. However, they state that more well controlled neuropsychological studies need to be conducted to determine the qualitative differences between the

dementing disorders. Even authors who have stated that there is insufficient evidence for the cortical/subcortical classification (Whitehouse, 1986; Brown & Marsden, 1988) acknowledge that methodological issues have limited previous studies.

Parkinson's and Alzheimer's disease and the cortical/subcortical classification

Especially controversial has been the classification of Alzheimer's (AD) and Parkinson's diseases (PD). The clinical and neuropathological evidence concerning the classification of these two disorders will be examined in more detail.

Neuropathology of Parkinson's disease. The primary neuropathology of Parkinson's disease (PD) has been well-established (Cummings, 1986). Lewy body development, neuronal loss, and dopaminergic deficits are changes characteristic of PD. Most of these changes are found in the substantia nigra, ventral tegmental area, and locus coeruleus. More limited and variable changes are also found in the nucleus basalis, caudate, putamen, globus pallidus. These structures are within the subcortical area of the brain and the brain stem. (Greenfield & Bosanquet, 1953; Den Hartog Jager & Bethlem, 1960; Javoy-Agid & Agid, 1980; Whitehouse, Hedreen, & White, 1983).

Studies of humans and animals with focal subcortical lesions have attributed specific neuropsychological

functions to subcortical structures (Cummings & Benson, 1984). Such lesions have been shown to produce disturbances of arousal, attention, mood, motivation, language, memory, abstraction, and visuo-spatial skills similar to those changes found in subcortical dementias. In contrast, the cognitive deficits which are characteristic of cortical degeneration, including agnosia, aphasia, and alexia, have not been associated with subcortical disorders unless there is diffuse effect with secondary cortical involvement. (Teuber,& Proctor, 1964; Ober & Divac, 1979; Penny & Young, 1983; Wallesch, Kornhuber & Kunz, 1983)

Although primary involvement of subcortical structures has been demonstrated in PD and associated with specific neuropsychological changes, some neuropathological research has indicated that the signs of degeneration which are common in AD (i.e. senile plaques and neurofibrillary tangles) can also be found in PD. Thus, some authors have suggested that dementia in PD is the result of cortical degeneration superimposed on subcortical degeneration, i.e. the co-occurrence of AD with PD (Boller, Mizutani & Roessmann, & Gambetti, 1980; Hakim & Mathieson, 1979; Gaspar & Gray, 1984).

However, there are a number of arguments weighing against the hypothesis that dementia in PD is simply co-occurring AD. First, there are studies that have failed to find an increase in these neuropathologic signs in PD (Ball,

1984). Instead, epidemiologic studies have found that PD and AD co-occur at a rate no greater than predicted by chance among the elderly population (Heston, 1991). Second, a correlation has been demonstrated between the degree of dementia and severity of motor dysfunction (bradykinesia and rigidity) suggesting a common underlying mechanism (Mayeux, Stern, & Rosen, 1981; Mortimer, Pirozzulo, & Hansch, 1982). Third, dementia has been demonstrated in PD patients that show neuropathological changes which are restricted to subcortical structure (Gaspar & Gray, 1984). Furthermore, MPTP-induced parkinsonism (synthetic neurotransmitter 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which produces almost a pure dopaminergic deficit by selective destruction of dopaminergic neurons in the substantia nigra (Burns et al., 1983), shows neuropsychological deficits consistent with subcortical dementia (Stern & Langston, 1985). This suggests that a pure dopaminergic deficiency is sufficient to produce subcortical dementia and that dementia in PD is not limited to cortical abnormalities. However, some suggest that co-occurring AD may account for the most severe cases of dementia among PD patients (Gaspar & Gray, 1984).

Neuropathology of Alzheimer's disease. The neuropathological signs which have been accepted as the hallmark of Alzheimer's disease (AD) are neurofibrillary tangles and senile plaques (Lezak, 1983). The neurofibrillary tangles are primarily found in the

hippocampal and amygdaloid areas of the brain located on the mesial temporal lobe (Lishman, 1978; Terry, 1978). Senile plaques are the product of neuronal degeneration and can be found throughout the cerebral cortex, especially in the parietal lobe. They are also found in the hippocampus and the amygdala (Roth, 1978). These changes have been associated with intellectual decline in Alzheimer's disease regardless of the age of the patient (Blessed, Tomlinson, & Roth, 1968). General atrophy has been identified through brain scans in the frontal and temporal lobes and in the anterior portion of the caudate nucleus (Bondareff, Baldy, & Levy, 1981). The reduction of acetylcholine-related enzymes in the cerebral cortex is also characteristic of AD upon post-mortem examination (Bowen, 1980). This neurotransmitter deficit has been correlated with the concentration of plaques in the cerebral cortex and with intellectual deficits (Perry, Tomlinson, & Blessed, 1978).

Despite the primary involvement of the cerebral cortex in Alzheimer's disease and the correlation with neuropsychological impairment, some argue against the classification of AD as a cortical dementia. This argument is based on evidence of degeneration of the nucleus basalis of Mynert (NBM), a subcortical structure, in some patients with AD (Whitehouse, Price, Clark, Coyle, & DeLong, 1981; Whitehouse et al., 1982). It has been suggested that the loss of cholinergic neurons in the NBM and it's cortical

projections could account for the cholinergic deficit and dementia of AD (Whitehouse et al., 1981; Whitehouse et al., 1982; Coyle, Price, & DeLong, 1983; Samuel, Terry, DeTeresa, Butters, Masliah, 1994)

Cummings and Benson (1984), however, assert that the classification of Alzheimer's disease as a cortical dementia should be maintained, based on the following arguments. First, the cortical/subcortical classification is a theoretical clinical concept, or a hypothetical construct, based on identifiable clinical features, not a precise anatomical concept. The clinical features of AD represent cortical dysfunction even if this is a result of loss of cholinergic input from a subcortical structure. Second, metabolic studies indicate extreme cortical hypometabolism with relatively normal subcortical metabolism (Foster, et al., 1984). Third, the degeneration of the NBM has been found in other diseases, including PD, Pick's disease, and traumatic basal injuries, that do not share the clinical characteristics of AD (Uhl, Hilt, & Hedreen, 1983; Salazar & Grafman, 1983; Whitehouse, Hedreen, & White, 1983). This means degeneration of the NBM is not consistently associated with the clinical features of AD. Fourth, the NBM in Parkinson's patients with dementia was not found to be different from the NBM of PD patient without dementia. Thus, it appears that degeneration of the NBM is not sufficient to produce dementia (Whitehouse et al., 1983).

Fifth, cholinergic neurons from the NBM connect to all areas of the cerebral cortex (Jones, Burton, & Saper, 1976), yet cholinergic deficits in AD occur primarily in the frontal and parietal areas. The primary motor, somatosensory, and visual areas are relatively preserved (Davies, 1978). Sixth, attempts at cholinergic therapy have effected some mild change in a small number of patients, but most continue to deteriorate (Etienne, Pastoor, & Gauthier, 1981; Renvoize & Jerram, 1979; Wettstein, 1983). This may indicate that other factors, such as cortical plaques and neurofibrillary tangles, may mediate cognitive changes.

Clinical distinction. As was stated above, proponents of the cortical/subcortical classification emphasize that this is a clinical or functional distinction. However, this clinical distinction has also been questioned because of inconsistent findings among studies that use neuropsychological measures (Whitehouse, 1986; Mayeux, Stern, Rosen, & Benson, 1983). In support of the cortical/subcortical classification, Huber and colleagues (1989) stated that the inconsistencies, when comparing neuropsychological results for different types of dementia, may be related to inaccurate diagnosis, failure to match patients for severity of cognitive impairment, use of different definitions of dementia, or methodological differences in neuropsychological assessment.

One of the important methodological problems in prior

neuropsychological studies is the use of measures such as intelligence tests or mental status examinations which were designed to confirm the presence of impairment or to detect the degree of impairment, but were not designed to detect differences between disorders (Cummings & Benson, 1984; Huber, Shuttleworth, Paulson, Bellchambers, & Clapp, 1986). On these tests, different groups of patients may achieve a similar level of impairment for different reasons. In order to distinguish the dementias, qualitative error analysis is needed. For example, qualitative differences have been found between cortical and subcortical dementias in the neuropsychological domain of memory. Although PD and AD patients both do poorly on tests of memory, PD patients perform poorly due to impairment in information organization and retrieval, and they benefit greatly from clues. Whereas, AD patients have severe encoding deficits and benefit minimally from clues (Caine, Ebert, & Weingartner, 1977; Pillon, Deweer, Agid, & Dubois, 1993; Tierney et al., 1994).

Thus, the essential question in this debate appears to be whether the clinical aspects of dementia in PD and AD are quantitatively different examples of the same syndrome, or whether they are qualitatively unique. Stern et al. (1993) addressed this question by comparing AD, demented PD, and non-demented PD groups to normal controls. Using this design, they were also able to address a related question,

whether changes with the onset of dementia in PD are qualitatively different from changes already demonstrated in non-demented PD, including word-finding difficulty, visuo-spatial dysfunction, and problems with some memory and executive functions (Dubois, Boller, Pillon, & Agid, 1991; Stern, 1987; Brown & Marsden, 1990; Raskin, Borod, & Tweedy, 1990). They found that although demented and non-demented PDs had some similarities, their performance also reflected some qualitative differences. Demented PD patients showed some impairments of memory similar to AD and significantly different from the non-demented PD group. Likewise, comparison of the pattern of cognitive deficits in AD and demented PD groups revealed similarities and differences. The demented PD patients performed more poorly on verbal fluency and visuo-spatial tasks, whereas the AD patients performed more poorly on delayed memory tasks. Thus, they concluded that dementia in PD was a combination of exacerbation of cognitive changes present in PD prior to dementia, and qualitatively different changes associated only with dementia. In addition, although the cognitive profiles of AD and PD with dementia showed similarities, a number of distinct clinical differences were inconsistent with the theory of dementia in PD reflecting concurrent AD.

The current study employed a design similar to that used by Stern et al. (1993) to focus on qualitative differences between PD with and without dementia, and AD.

Differences between AD and PD on visuo-spatial and conceptual skills

Qualitative differences have been demonstrated between dementia of AD and PD in the domains of memory and language (Huber et al., 1989; Bayles & Tomoeda, 1983; Helkala, Laulumaa, Soininen, & Riekkinen, 1988; Kramer, Levin, Brandt, & Delis, 1989; Randolph, Braun, Goldberg, & Chase, 1993; Sullivan, Sagar, Gabrieli, Corkin, & Growdon, 1988, Stern et al., 1993; Tierney et al., 1994; Pillon et al., 1993). However, there are few studies comparing visuo-spatial and executive functioning of AD and PD.

In regard to visuo-spatial functions, both AD and PD have been found to be impaired on general measures, such as the Verbal-Performance difference on the Wechsler Adult Intelligence Scales (Brown & Marsden, 1988). However, such general measures do not indicate the nature of the visuo-spatial impairment. Brown and Marsden described a need for specific areas of visuo-spatial functioning to be examined in more detail using comparative studies. One specific type of visuo-spatial ability is visuo-constructive performance (drawing to verbal command or copying a line drawing). Comparative studies of AD and PD on visuo-constructive measures are lacking, however, there are a few studies of these functions in AD or PD alone. One study of Parkinson's patients copying the Rey-Osterreith Complex Figure found PD patients to be impaired in drawing main features in an