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PSYCHOLOGICAL FACTORS AND PET MEASURED GLUCOSE METABOLISM IN OLIVOPONTOCEREBELLAR ATROPHY

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We compared 29 olivopontocerebellar atrophy (OPCA) patients on psychiatric rating scales, cognitive tests, and positron emission tomography to 12 normal volunteers with similar age and sex distributions. The patients were generally comparable to normals in cognitive function, but poorer on psychomotor tasks. They had significantly different scores on formal self-report scales than the normals, indicating a greater degree of self-complaint. Analyses of the components of self-complaint suggested that illness-related concerns accounted for most of the differences between the groups. The magnitude of self-complaint was significantly and specifically correlated with the level of glucose metabolism in the frontal cerebral cortex of OPCA patients. These results may be attributed to a combination of biological and experiential factors. The level of patient complaint may be influenced by organic brain dysfunction reflected in metabolism and emotional disturbance, whereas the content of complaint may be specific to the individual's situational experience.

Olivopontocerebellar atrophy (OPCA) is a progressive neurological disorder that occurs both sporadically and with hereditary transmission. It is characterized by neuronal degeneration in the cerebellar cortex, pons, and inferior olives, although lesions in other central nervous system (CNS) locations have been described as well. OPCA may not represent a single morbid entity, but it is viewed as a useful term because of its practical utility in differential diagnosis. A persistent question in the study of OPCA is concerned with the nature and extent of the behavioral impairments other than motor disturbances that occur in this disorder. We previously reported an absence of memory impairment in OPCA, but other investigators (Kish et al., 1988, 1994) have reported a range of cognitive and other neuropsychological deficits in ataxia. When cognitive impairment is reported, it remains unclear if a

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causative relationship exists between OPCA and dementia (e.g., as defined in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, 1994, pp. 133-139; Berent et al., 1990; Kish et al., 1994). Neuropsychological impairment in OPCA might result from cortical or subcortical pathology or a combination of the two (Kish et al., 1988, 1994). The dementia could be due to a comorbid condition and its occurrence, if due to OPCA, could depend upon the particular sample of patients studied (e.g., their genetic history). Gilman et al. (1994), for example, reported that sporadically occurring OPCA may follow a course of disease progression that differs from genetically transmitted OPCA and that eventuates in multiple system atrophy (MSA).

One question concerning cognitive function in OPCA relates to the extent that motor impairment interferes with task performance in the neuropsychological examination, thereby, slowing response times and leaving the patient appearing more cognitively disabled than is actually the case. We previously reported, for example, that impairments in motor function contribute importantly to cognitive symptoms in OPCA (Berent et al., 1990). Psychomotor slowing is often associated with emotional disturbance as well, and we reported finding greater levels of depression and anxiety in OPCA patients than in volunteer controls (Berent et al., 1990). This finding is consistent with observations in Parkinson's disease (PD), a disorder similar to OPCA in some respects, where depression was found to be more prevalent in PD patients with instability of gait and prominent bradykinesia (i.e., presumably patients with greater motor involvement in their presenting clinical picture) than in tremor-dominant patients (i.e., patients exhibiting a more restricted involvement of motor symptoms; Cummings, 1992). In Huntington's disease (HD), another neurological disorder that involves substantial motor impairments, depression is very common, often preceding other symptoms of the disease and occurring in up to 40% of patients (Mayberg et al., 1992).

A neurological disease model provides an effective tool for studying psychological disorders, such as affective disturbance, because specific neuroanatomical abnormalities are usually identifiable. As emphasized by Flint and Eastwood (1988), patients with dysfunction of frontal brain regions often present with symptoms that are similar to depression, and many writers have employed a disease model to report a relationship between frontal, mesocortical-frontal connections, or both, and affective disorder (Baxter et al, 1989; Buchsbaum et al., 1986; Cummings, 1992, 1993; Dolan, Bench, Brown, Scott, & Franckowiak, 1994; Mayberg et al., 1990, 1992; Ring et al., 1994; Seidenberg, Hermann, & Noe, 1996). It is important to note that when Bench, Franckowiak, and Dolan (1995) studied 40 patients with major depression and demonstrated that recovery from depression in these individuals was accompanied by increases in cerebral blood flow in the same areas that evidenced decreased blood flow during the depressed state.

Positron-emission tomography, or PET, is still a relatively new but tremendously exciting technique that allows for imaging of the brain in the intact organism. PET differs from other imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), in the important distinction that the image produced in PET is a functional as opposed to a structural picture of the brain. PET is a technique for measuring radioisotope concentrations in regional brain tissue and can be used to quantify the brain's metabolic activity in response to a host of chemical agents. This advance allows for measurement of such physiological variables as oxygen or glucose consumption in specified regions of brain and, in turn, provides an opportunity to study relationships between psychological factors and these important biological phenomena. Previous studies using PET to measure glucose metabolism, for example, have demonstrated a relationship in both PD (Mayberg et al., 1990) and HD (Mayberg et al., 1992) between measures of depression and degree of hypometabolism in frontal regions of the brain.

The present study was developed to investigate the presence and nature of emotional and cognitive disturbance in OPCA by comparing OPCA

patients to nonaffected volunteers in their neuropsychological test performance and responses to self-reported psychiatric rating scales and to relate these observations to brain metabolism as studied with PET. We hypothesized that patients with OPCA would perform similarly to normals on cognitive tests, but evidence greater psychomotor impairment and emotional self-complaint than healthy control participants. It was further proposed that the degree of patients' emotional disturbance, as measured by their self-report, would correlate specifically to the degree of flourodeoxy glucose (FDG) metabolism in frontal brain regions. We sought also to compare results between sporadic and hereditary forms of OPCA.

Method

Participants

Participants in these studies were 29 OPCA outpatients (i.e., 13 men, 16 women) and 12 normal controls (i.e., 5 men, 7 women). Patients and controls were selected from a larger population (i.e., 39 patients, 25 controls) on the basis of education and intellectual levels. This population was restricted a priori to include only patients and controls with an average range of intellect (e.g., Wechsler Adult Intelligence Scale–Revised Full Scale IQ; WAIS-R FSIQ > 80 < 120; Wechsler, 1981) and an education level of 10th grade or higher. This restriction was necessary because of the nature of the study, that is, reading and self-report were necessary for participation. Four patients were excluded because of low intellect, and six others were excluded either because of low educational achievement, physical inability, or refusal to participate in the study protocol. Because OPCA is a disorder with usual onset in adult life, additional disease factors are most likely explained by educational, or even intellectual, insufficiencies in those OPCA patients who were excluded.

The patients and controls were participating in an ongoing study of OPCA that uses [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) and PET. The patients had a mean age of 53.2 years (SD = 12.2), and for controls the mean was 47.6 years (SD = 12.2). The mean education level for patients was 13.3 years (SD = 2.5) and for controls it was 14.9 years (SD = 2.3). The groups did not differ significantly in age, t (39) = 1.35, *ns*, or education, t (39) = -1.91, *ns*, or in terms of WAIS-R Vocabulary, t (39) = -1.06, *ns*, or prorated FSIQ, t (39) = -1.76, *ns*. This work was approved by the Human Use Committee of the University of Michigan Medical Center and informed consent was obtained from each participant prior to the study.

For part of the analyses, we divided the patients, based upon patient history, into a sporadic OPCA (sOPCA; 6 men, 10 women) group and a dominantly inherited OPCA (dOPCA; 4 men, 8 women) group with one patient remaining unclassified. The sOPCA group (M = 58.9 years, SD = 8.4 years) was significantly older than the dOPCA group (M = 45.8 years, SD = 13.4 years), t (26) = 3.18, p = .004. No significant difference in years of education was noted between the sOPCA group (M = 12.9, SD = 2.26) and dOPCA group (M = 14.0, SD = 2.8), t (26) = 1.11, *ns*.

Clinical diagnoses

The normal controls had no history of neurologic or psychiatric disease and no significant abnormalities were discovered on neurologic and general physical examination. OPCA was diagnosed on the basis of the history, physical examination, neurologic examination, laboratory tests to exclude other disorders, and the findings from CT scans, MRI scans, or both. None of the patients or normal controls were taking medications known to affect CNS function directly or indirectly. No malignancy was detected in any patient, and none of the patients were alcoholics or other substance abusers.

Behavioral measures

Test measures were selected to reflect major categories of behavior, consisting of general intellect, cognition (e.g., language and memory), psychomotor ability, affect, and psychopathology. All tests were administered in a standardized fashion by trained technicians who were uninformed of the exact diagnoses of the persons being tested. Measures of neuropsychological performance reflected three groupings: (a) selected age-corrected subtests from the WAIS-R; (i.e., Arithmetic, Vocabulary, Digit Symbol, Picture

Completion, Block Design, Picture Arrangement), (b) the Russell-Modification Wechsler Memory Scale (WMS-R; Wechsler, 1945; Russell, 1975), and (c) a battery of motor component tasks (i.e., Finger Tapping Speed, Grooved Pegboard, Strength of Grip, and Simple and Choice Reaction Time, cf., Lezak, 1995). Because the study is part of an ongoing project, we were obligated to employ measures that were part of that protocol, that is, the WMS rather than the Wechsler Memory Scale–Revised (WMS-R; Wechsler, 1987). A standard, partial WAIS-R was used to estimate FSIQ (see Silverstein, 1982).

Two self-report type inventories were used to rate psychological complaints, the Symptom Checklist-90–Revised (SCL-90-R; Derogatis, 1994) and a self-rating scale (SRS; Berent, Boll, & Giordani, 1982). Participants rated themselves on the SRS on nine dimensions. The individual subjectively rates each of the nine dimensions on a scale ranging from 1 to 5. The rated categories were sadness, sense of personal power, sleepiness, shame, confusion, feeling sick, hopelessness, boredom, and restlessness. The individual scales were then summed to yield an overall score. This overall score can range from 9 to 45. A relatively low SRS overall score indicates greater complaint, whereas a higher score reflects less complaint.

The SCL-90-R is a 90-item self-report symptom inventory that was designed to reflect the psychological symptom patterns of medical patients (Derogatis, 1977). The scale consists of nine primary symptom dimensions and three global indexes of distress. The dimensions and indexes reflect somatization (SOM), obsessive-compulsive tendencies (OC), interpersonal sensitivity (IS), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), psychoticism (PSY), global severity index (GSI), and a positive symptom distress index (PSDI). A relatively high score on the SCL-90-R reflects greater complaint.

The PET procedure

Patients and normal participants were studied while lying supine, awake, and blindfolded in a quiet room. Scans were performed with a TCC PCT 4600 A tomograph and were made 30 to 75 min after intravenous injection of 10 mCi of [18F]FDG. Regions of interest (ROIs) were studied in the brainstem, cerebellar vermis, cerebellar hemispheres, thalamus, basal ganglia (i.e., caudate nucleus and putamen), and cerebral cortex. Levels comprising each ROI were contiguous. PET images were viewed in the transverse and sagittal planes. Data were collected from transverse sections with the following: (a) a 2.6 cm^2 polygon over each cerebellar hemisphere from 4 of the 20 levels, (b) a 2.1 cm^2 rectangle over the vermis from 2 of 20 levels, (c) a 1.7 cm^2 rectangle over the brainstem from 2 of 20 levels, (d) a 1.3 cm^2 parallelogram over each thalamus from 2 of 20 levels, (e) a 0.9 cm^2 square over each caudate nucleus from 2 of 20 levels, and (f) a 1.9 cm^2 parallelogram over each putamen from 2 of 20 levels. Each ROI was automatically centered over a local peak in local cerebral metabolic rate for glucose (lCMRGlc). ROIs from the cerebellar vermis were posterior to the fourth ventricle. The brainstem ROI chiefly reflects the pons, but the mesencephalon could be partially represented.

Data from the cerebral cortex were obtained in transverse images by measuring lCMRGlc in the cortical ribbon from six consecutive planes beginning with the plane containing the most superior portion of the cingulate gyrus and continuing inferiorly to the plane containing the lowest portion of the thalamus. This was accomplished with an algorithm that detects the outer edge of the cortical rim from an image that has been passed through a contrast-enhancing filter. The algorithm then identifies on the original image a cortical band that extends inward from this edge until either the metabolic rate drops below the value on the outer edge of the rim or the band reaches a width of 15 mm. An area-weighted mean metabolic rate was computed for the mean cortical value. At each level, the cortical band was divided into eight equal-arc sectors for each hemisphere. Frontal cortex regions were composed of the two anterior most sectors in each hemisphere and in the occipital cortex, the two most posterior sectors. Normalized values were obtained by dividing individual ROI values by the mean value from the

cerebral cortex over all slices. Technical factors precluded PET data being collected from four patients and occipital cerebral metabolic rate from four normal controls.

Statistical analyses

In addition to standard descriptive statistics (e.g., *M*, *SD*), analyses included Pearson product-moment correlation, Hotelling's multivariate analysis of variance (MANOVA), and univariate *t* tests. Considering the number of MANOVAs and univariate analyses completed, a conservative alpha level of .025, rather than the traditional .05 level, was used for determining significance on all statistical tests.

Results

Hotelling's MANOVA procedure was applied to the three categories of variables presented in Table 1. Overall MANOVAs were found to be significant for select WAIS-R variables, F (6, 32) = 1.01, p = .0006, and the psychomotor measures, F (6, 29) = 1.67, p = .0001. Results of subsequent univariate tests (and *M*s, *SD*s) are listed in Table 1 to show specific differences. With an alpha level of .025, patients were significantly slower on a finger tapping task, grooved pegboard performance, and simple, but not choice, reaction times. Strength of grip measured in a standardized fashion with a mechanical dynamometer was also significantly

Table 1
Intellectual, Cognitive, and Psychomotor Performance for OPCA Patients and Normal Participants

	OPCA[a]		Normal[b]		
Variable	*M*	*SD*	*M*	*SD*	*p*
WAIS-R FSIQ[c]	98.52	9.59	104.17	8.61	*ns*
Arithmetic	10.57	2.29	10.33	1.37	*ns*
Vocabulary	10.03	2.21	10.83	2.13	*ns*
Digit Symbol	7.04	2.44	10.00	2.66	.002
Picture Completion	9.04	2.00	10.17	1.80	*ns*
Block Design	8.85	2.14	11.50	2.51	.002
Picture Arrangement	10.00	2.82	10.33	2.84	*ns*
Wechsler Memory Scale					
Information	5.10	0.94	5.58	0.67	*ns*
Orientation	4.79	0.68	5.00	0.00	*ns*
Mental Control	6.27	1.93	7.75	1.22	*ns*
Logical Memory	8.62	2.33	10.00	2.02	*ns*
Digit Span	11.17	1.79	11.33	2.43	*ns*
Visual Reproduction	9.75	2.33	11.08	2.30	*ns*
Paired Associates	15.33	3.31	18.13	2.93	*ns*
Logical Memory % recall	80.10	17.82	79.17	11.95	*ns*
Visual Reproduction % recall	82.57	21.37	87.25	18.70	*ns*
Motor Component Tasks					
Finger tapping speed[d]	27.24	6.90	43.93	7.89	.0001
Grooved pegboard[d] (s)	192.85	75.66	65.83	5.80	.0001
Grip strength[d] (kg)	23.59	9.29	32.52	11.48	.01
Simple reaction time (ms)	414.04	115.96	313.75	52.48	.007
Choice reaction time (ms)	505.89	92.15	442.08	82.01	.04

Note. OPCA = olivopontocerebellar atrophy; WAIS-R FSIQ = Wechsler Adult Intelligence Scale–Revised Full Scale IQ.
[a]n = 29. [b]n = 12. [c]FSIQ prorated from four subtests (Silverstein, 1982). All subtest scores are age-corrected. [d]Average of both hands.

lower in the patients than in the controls. Among the WAIS-R variables, only scores for Digit Symbol and Block Design were found to differ significantly between the groups. Given the strong differences between patients and controls on motor-related measures, the WAIS-R variables were again analyzed using Finger Tapping Speed as a covariate, and the findings were no longer significant for Digit Symbol, F (1, 35) = 3.00, *ns*, and Block Design, F (1, 35) = 1.74, *ns*. The MANOVA for the WMS comparisons was not significant, F (9, 30) = 0.22, *ns*.

Few differences between the groups were noted on measures of "higher" intellectual processes including memory (e.g., 30 min delayed recall of verbal, scale IV, and visual, scale VI tasks from the WMS). Despite their relatively severe motor symptoms, the patients' performance on these memory tasks was similar to that of the controls. For example, the patients, on average, recalled 7 of 9 initially learned verbal items after 30 min as compared with 8 of 10 for the controls, and patients recalled 8 of 10 visual items after 30 min versus 10 of 11 over the same time period for the controls.

PET results are similar to those reported previously (Gilman et al., 1988; see Table 2). The MANOVA for the category of metabolic measures was significant, F (5, 31) = 2.06, p = .0001, and subsequent univariate analyses (and *M*s, *SD*s) are reported in Table 2. In comparison to the normal controls, the OPCA patients evidenced reduced glucose metabolic activity in the cerebellar hemispheres, cerebellar vermis, and brainstem. Other portions of the brain appeared to be normal in metabolic rate.

Patients reported a higher level of psychological complaint on the SRS than did controls, t (39) = -2.42, p = .02 (see Table 3). Mean scores and standard deviations for individual items on the SRS were also compared and are presented in Table 3. The multivariate test for the participants' ratings of complaints and symptoms on the SCL-90-R was significant, F (11, 28) = 1.20, p = .008, and univariate comparisons (and *M*s, *SD*s) are listed in the Table 4.

Patients' self-ratings were significantly correlated with the level of cerebral metabolic rate in the frontal cerebral cortex (see Figure 1), r (23) = .54, p = .005, but not in other regions of the cortex. A similar relationship between frontal metabolism and self-ratings was not found in the normal control group, r (10) = -.05, *ns*.

With regard to dividing the patients into sporadic and hereditary types, no difference was found in terms of general intellect between the groups, for sOPCA, M = 98.06, SD = 10.43, for dOPCA, M = 100.25, SD = 8.38, t (26) = -0.60, *ns*. sOPCA patients, however, did perform more poorly on verbal and visual initial learning tasks than did dOPCA patients. For the WMS Paired Associate Learning score for groups sOPCA (M = 14.12, SD = 3.52) and dOPCA (M = 17.17, SD = 2.15), the

Table 2
Local Metabolic Rate for Glucose, [^{18}F]FDG, for OPCA Patients and Normal Participants

Region	OPCA[a]		Normal[b]		
	M	*SD*	*M*	*SD*	*p*
Brain stem	0.59	0.08	0.75	0.04	.0001
Vermis	0.66	0.14	0.92	0.10	.0001
Cerebellar hemispheres	0.74	0.12	1.02	0.11	.0001
Thalamus	1.17	0.11	1.19	0.08	*ns*
Frontal	1.01	0.04	1.01	0.02	*ns*
Occipital[c]	0.96	0.06	0.92	0.06	*ns*

Note. [^{18}F]FDG = [^{18}F]-2-flouro-a-deoxy-D-glucose; OPCA = olivopontocerebellar atrophy.
[a]n = 25. [b]n = 12. [c]Values for four participants could not be obtained due to technical difficulties.

test was nonsignificant, t (26) = -2.64, p = 01. For the WMS Visual Reproduction score for groups sOPCA (M = 8.52, SD = 1.95) and dOPCA (M = 11.04, SD = 1.71), the test was also nonsignificant t (26) = -3.57, p = .001. No differences were observed on visual- or verbal-delayed recall or other neuropsychological measures. Both sOPCA and dOPCA patient groups appeared to be comparable in their ratings of emotional disturbance and self-complaint, and both groups reflected a strong, positive relationship between self-ratings and frontal hypometabolism.

Table 3
Scores on Self-Rating Scale (SRS) for OPCA Patients and Normal Participants

	OPCA[a]		Normal[b]		
Self-Rating Scale	*M*	*SD*	*M*	*SD*	*p*
Total score	35.93	6.26	40.75	4.45	.02
Sadness	4.55	0.78	4.58	0.67	*ns*
Power	3.27	1.38	4.00	0.95	*ns*
Sleepiness	4.24	1.12	4.33	1.30	*ns*
Shame	3.96	1.02	4.50	0.67	*ns*
Confusion	4.24	1.09	4.58	0.79	*ns*
Sickness	3.93	1.38	4.75	0.62	.04
Hopefulness	3.45	1.57	4.75	0.45	.008
Boredom	4.31	0.85	4.75	0.62	*ns*
Restlessness	3.97	1.24	4.50	0.67	*ns*

Note. OPCA = olivopontocerebellar atrophy.
[a]n = 29. [b]n = 12.

Table 4
Scores on the SCL-90-R for OPCA Patients and Normal Participants

	OPCA[a]		Normal[b]		
Subscale	*M*	*SD*	*M*	*SD*	*p*
Global severity index	44.52	9.05	38.73	5.27	.05
Positive symptom distress index	46.24	8.93	36.46	5.88	.0002
Somatization	49.28	10.16	45.64	7.39	*ns*
Obsessive-compulsive	46.48	8.79	42.36	6.14	*ns*
Interpersonal sensitivity	46.69	10.52	42.27	6.44	*ns*
Depression	44.86	8.99	38.36	6.58	.03
Anxiety	43.24	9.28	38.27	4.79	*ns*
Hostility	42.48	9.75	42.82	7.67	*ns*
Phobic anxiety	46.93	11.49	38.36	8.37	.05
Paranoid ideation	42.89	10.02	42.36	3.75	*ns*
Psychoticism	46.38	8.29	36.09	5.59	.0005

Note. SCL-90-R = Symptom Checklist-90–Revised; OPCA = olivopontocerebellar atrophy.
[a]n = 29. [b]n = 12.

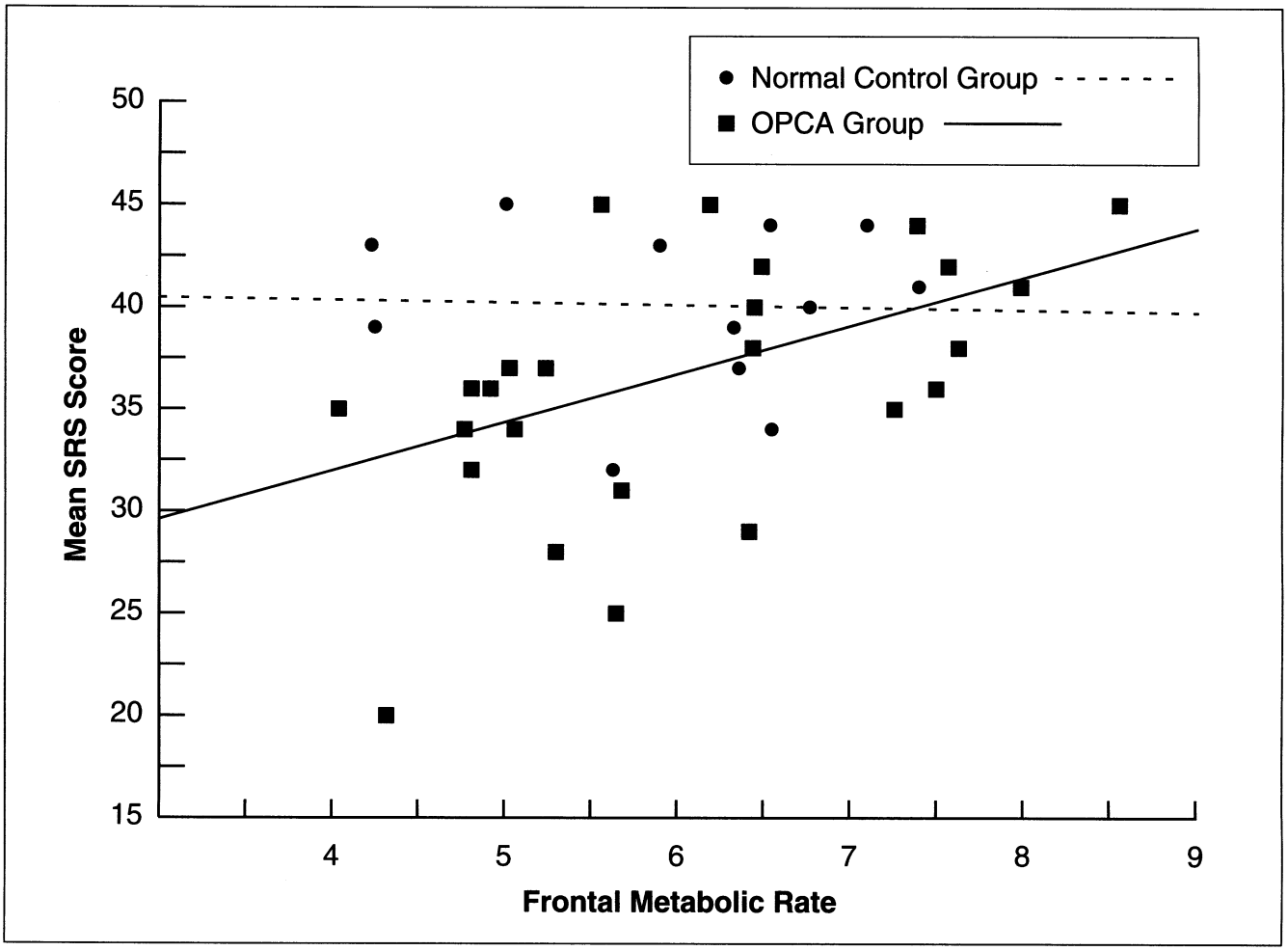

Figure 1. Relationship between self-rating score (SRS) and cerebral metabolic rate for glucose in the frontal lobes of olivopontocerebellar atrophy (OPCA) patients, r (23) = .54, p = .005, and normal controls, r (10) = –.05, *ns*.

Discussion

Results confirmed our primary hypotheses. Reflecting the symptomatic nature of the disorder, the patients with OPCA in this study performed more poorly than normals on psychomotor tasks (e.g., finger tapping), but they performed normally on cognitive tasks (e.g., learning and memory). On tests with both cognitive and motor components (e.g., WAIS-R Block Design and Digit Symbol), the patients performed more poorly than normals, although these results appeared to be accounted for primarily by the patients' motor impairment. At the same time, patients rated themselves as having greater psychological disturbances than the normals. The level of complaint reflected in these ratings was found to correlate significantly with metabolism in frontal brain regions in patients with higher complaint being associated with relative lower metabolism and less complaint with higher metabolism. This relationship appeared to be specific to the frontal regions and was not observed in the normal volunteers. Although there was a tendency for sporadic patients to perform more poorly on some tasks than did patients with hereditary transmitted disease, differences were not generally significant.

The self-ratings of some individual patients were as high as those of patients with formal psychiatric diagnoses. Affect (i.e., depression) was a common type of disturbance seen in the patients' ratings.

On the SRS, the patients rated themselves lowest (i.e., most complaint) on the "power" dimension, next lowest on "hopelessness." Patients had the least complaint on the "sadness" item and the next least complaint on the three items, sleepiness, confusion, and boredom.

Depression in PD, a disorder with similarities to OPCA (Colosimo, Albanese, Hughes, Bruin, & Lees, 1995), has been described by Cummings (1992) as being distinguishable from other depressive disorders by the presence of greater anxiety and less self-punitive ideation. OPCA patients in the present study produced self-ratings that appear to be related to concerns they hold regarding their medical condition. At the same time, there is a lack of emphasis in the self-report of these patients on feelings of sadness. The minimal indications of vegetative disturbances, too, leave the OPCA patients appearing dissimilar to individuals who suffer from depressive disorders as described in psychiatric diagnostic manuals (e.g., *DSM-IV*, 1994). Observations that emotional disturbance accompanying known neurological illnesses may differ phenomenologically from other psychiatric conditions are intriguing because they raise the possibility of differing neural substrates between affective disorders. It is also conceivable, however, that a common neural system underlies all affective disturbance with apparent dissimilarity in symptoms reflecting existential differences between patients. These points are discussed further later in this article.

A strong positive relationship was observed between behavioral symptoms as reflected in the patients' overall self-ratings and the absolute level of cerebral cortical metabolism specifically in the frontal lobes. The correlation appeared to be specific to the patient group, because it was not present in normal volunteers. Nor was a significant correlation found between ratings and metabolism in the other regions of the cerebral cortex. The frontal area of the brain and its connections to basal ganglia and the limbic system, in general, have served importantly in a number of propositions about the physiological bases of psychopathology (e.g., Mayberg et al., 1990; 1992). In the present study, PET data were obtained using our original scanner. A recent study from our institution using a newer scanner with higher resolution found more widespread hypometabolism in OPCA than reported here (Gilman et al., 1994). Replicating the present study with this new, higher resolution scanner will allow us to address, in greater detail than here, the question of frontal lobe involvement in emotional disturbance. A future study might also profit from a direct comparison between psychiatrically depressed patients and patients with neurological illness accompanied by emotional complaints. Nothing that has been said is meant to imply that conditions underlying the self-complaints of the patients under study are not potentially debilitating. Clinically, each case will need to be evaluated on its own merits and decisions about treatment interventions made accordingly.

Due to the relatively small number of patients and the significant difference in age, we are unable to place emphasis on the differences observed between patients with sOPCA versus those with dOPCA. There was a tendency for the sporadic patients to perform more poorly on some tasks, especially in the area of learning (both verbal and visual). Because the groups were comparable in self-report, emotional disturbance would not seem to explain these differences in performance. It has been reported (Gilman et al., 1994) that sOPCA patients follow a course of disease progression that differs from those with dOPCA and eventuates in MSA. It may be that inconsistencies reported in the literature concerning cognitive functioning in OPCA patients derive from genetic or other variations in study samples between investigations. Family history as well as other individual differences between patients should be closely monitored in future work.

The relationship observed between patient self-report and frontal metabolism makes it tempting to speculate about possible frontally mediated behavioral functions in the role of emotional disturbance in these OPCA patients. Not only is it prudent to avoid invoking causal implication in correlational observations, the lack of significant hypometabolism in the frontal region calls for explanation. Also, countering the observed

relationship between our behavioral and physiological measures is the strong reactive nature of the self-report content (e.g., patient concerns about loss of control and severity of medical disorder). Are we seeing cases of pathophysiology driving an emotional response, or instances of experience affecting metabolism at a site of cognitive mediation? Perhaps the answer lies in a combination of these two possibilities.

To be specific, the present findings are consistent with other studies cited earlier, all of which report a positive relationship between emotional symptoms and frontal brain regions. The neurological conditions studied to date (e.g., PD, HD, and OPCA) all involve motor symptoms and subcortical system dysfunction at some point in the course of disease progression. It has been proposed that frontal regions of the brain might become involved in these conditions secondarily via connections to other brain regions, and that these other, primary sites of abnormality might include regions that regulate emotion (e.g., Seidenberg et al., 1996). Monoamines (e.g., dopamine, serotonin) have been implicated in both motor disorders and depression (Trimble, 1988). The monoamines have also been identified as neurotransmitters in the CNS, and they reflect the neuroanatomical distribution needed to connect subcortical regions of the brain to the frontal cortex (Gilman & Newman, 1987). If level of patients' self-complaint in the present study was driven by subcortical or mesocortical abnormalities reflected through neurochemical connections to frontal brain regions, we might expect the observed relationship between self-complaint and the frontal regions despite the presence in this area of normal levels of metabolic activity. We might also expect, in such a scenario, a divergence between level of complaint and content of complaint (i.e., a reflection of the affected patient's experience). Discontinuity between the intensity of mood and its content could also explain phenomenological differences that might exist between affective disturbance in neurological disorders, such as OPCA, and those seen in psychiatric illnesses. We speculate that the levels of complaint made by the patients in the present study were influenced by organic brain dysfunction reflected in metabolism and emotional disturbance, whereas the content of complaint remained specific to an individual's situational experience.

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