Clinical, Motor, and Biological Correlates of Depressive Disorders After Focal Subcortical Lesions

Edward C. Lauterbach, M.D.
Joseph G. Jackson, M.D.
Spencer T. Price, B.S.
Ami N. Wilson, B.A.
Alan D. Kirsh, M.D.
G.E. Alan Dever, Ph.D.

The authors studied depression after focal subcortical lesions (SCLs) in 45 highly selected subjects. Secondary major depression (2°MD) occurred in 20.0%, depressive disorder NOS (2°DDNOS) in 4.4%, and 2° dysthymia in 0.0%. 2°MD after SCLs was associated with pallidal lesions (88.9%) and dystonia without geste antagonistique; subjects with 2°DDNOS had nigrotegmental lesions and parkinsonism. Depressive severity after SCLs correlated positively with severity of parkinsonism and dystonia. Pallidal lesions disrupting neurotransmitter systems and pallidothalamic and parietal input to the frontal lobe may lead to 2°MD, whereas nigrotegmental lesions may predispose to 2°MD forme fruste (2°DDNOS) through disruption of mesocortical frontal or nigrostriatal dopamine tracts. Patients should be closely followed over several years for depression after such lesions, especially when accompanied by parkinsonism or dystonia without geste antagonistique.

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Depression has been correlated with certain clinical, anatomical, pharmacological, and physiological disturbances. A variety of data suggest depression may be associated with basal ganglia disorders including Parkinson's disease[1–12] (PD), idiopathic dystonia[13–19] (ID), and basal ganglia lesions.[20–23] The emerging pathophysiology of depressive disorders suggests important roles for dopamine[24,25] and physiological interaction between different brain regions in depression.[25] These disturbances might directly evoke clinical depression through physiological consequences, or they might produce clinical disabilities that eventuate in depression through psychosocial mechanisms.[26,27] Regardless, depression may relate to clinical features, lesion anatomy, dopaminergic function, and physiological interaction between distinct brain circuits. Investigation of these factors may yield important clues to the nature of depression.

We have been interested in the relation of depression to subcortical circuitry and clinical neuropsychiatric features. We therefore studied subjects with selective focal subcortical lesions (SCLs) that disrupt this circuitry. These SCLs also often evoke certain clinical neuropsychiatric features of interest, including parkinsonism and dystonia, which can occur after SCLs of the substantia

Received September 12, 1995; revised April 11, 1996; accepted April 24, 1996. From the Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine, Macon, Georgia. Address correspondence to Dr. Lauterbach, Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine, 1550 College Street, Macon, GA 31207-0001.

nigra and basal ganglia. Consequently, we studied the relationship of depression to subcortical circuit disruption and these clinical neuropsychiatric findings in subjects with circumscribed SCLs. We endeavored to determine which subcortical structures, subcortical circuits, and clinical features were associated with depression in our subjects.

Specifically, we analyzed the frequency of DSM-III,[28] DSM-III-R,[29] and DSM-IV[30] major depression with first onset occurring before (1°MD) or after (2°MD) SCL onset. We focus on 2°MD here because of our interests outlined above. We also examined the frequency of other 2° depressive disorders: depressive disorder not otherwise specified (2°DDNOS) and dysthymia. We compared our rate of 2°MD after SCLs to the rate of MD in matched normative controls and to the rates for 2°MD in identically studied consecutive subjects with two different clinically recognizable basal ganglia disorders, PD and ID. We also compared this rate of 2°MD after SCLs with external control rates of 2°MD after parietal lobe and left frontal infarcts. Next, we surveyed the lesion loci in 2° depressive disorders. Finally, we ascertained whether the observed rate of 2°MD in this select sample exceeded chance alone and examined disabling clinical variables (2° parkinsonism and 2° dystonia) that might be associated with depressive severity in this select SCL sample.

We hypothesized that:

1. The prevalence of 2°MD after SCLs exceeds the rate expected for normative populations.
2. Parkinsonism severity is greater in SCL subjects with more severe depression.
3. Dystonia severity is greater in SCL subjects with more severe depression.
4. Dystonia with geste antagonistique occurs less frequently in 2°MD than in SCL subjects with 1°MD.

We were interested in testing these hypotheses because 1) 2°MD after SCLs should be more common than normative rates if the depression is truly a consequence of the lesion; 2) although primary PD and ID may be associated with 2°MD in general, this may not prove to be true of our sample of SCLs with 2° parkinsonism or 2° dystonia; 3) parkinsonism is associated with disruption of limbic dopamine supply;[24,31] and 4) dystonic geste antagonistique represents a novel clinical variable associated with reduced symptom control and the inability to modulate motor outflow by sensory input.[32] (*Geste antagonistique* refers to postures and other sensory tricks adopted to alleviate dystonic contractions,[32] probably requiring the physiological interaction of parietal sensory and frontal motor regions of the brain.)

METHODS

Sample Selection

We reviewed 10,000 MRI files (1.5-tesla GE Signa MRI scanner) from our Department of Radiology library at the Medical Center of Central Georgia to find suitable subjects with SCLs. All MRIs had been obtained on patients for clinical purposes by their physicians. Radiologists' findings were reviewed for evidence of focal SCLs limited to the basal ganglia (BG), thalamus, or cerebellum (CB). All SCLs represented lacunar infarcts or similar lesions. Unidentified bright objects ("UBOs"), diffuse white matter hyperintensities, and other artifacts were not considered as SCLs. To prevent selection bias, all films were reviewed by raters blind to subject condition, psychiatric diagnosis, neurological diagnosis, medical diagnosis, and reason for referral for MRI scan.

The selected 120 subjects' films were then reexamined by a radiologist and a neuropsychiatrist. Stringent exclusion criteria eliminated significant periventricular white matter hyperintensities or additional pathology (such as cortical atrophy or other lesions) outside the BG, CB, or thalamus evident on either T_1- or T_2-weighted images. After applying the above criteria, 27 subjects were now excluded because of additional minor findings not noted in the initial clinical report. We then attempted to contact the remaining 93 subjects by using locating information from medical records charts, billing offices, and county tax records. Forty-five subjects agreed to be studied, 23 declined, 11 were definitely deceased, and 14 could not be contacted, presumably either because of death, nursing home placement, or having moved out of the county.

Procedures

All 45 subjects provided written informed consent on an Institutional Review Board–approved informed consent form after the procedures had been fully explained. Subjects were then entered into the study, which consisted of a clinical diagnostic psychiatric interview; structured diagnostic interviews using the Diagnostic Interview Schedule for DSM-III[33] (DIS) and the Structured Clinical Interview for DSM-III-R[34] (SCID); standardized mental status exam (Mayeux et al.–modified[35] mental status exam of Folstein et al.[36]); Hamilton Rating Scale for Depression[37] (Ham-D); routine neurological exam; movement disorder clinical exam; and a standardized movement disorder interview and exam including the Unified Parkinson's Disease Rating Scale[38] (UPDRS), Hoehn and Yahr staging,[38] PD dyskinesia scale, Dystonia Disability Scale[39] (DS), and Dystonia Movement Scale[39] (DMS). No subjects were taking neuroleptics or other agents that might influence evalu-

ation. Subjects were assessed for a variety of DSM-III and DSM-III-R psychiatric disorders, and it was determined by history and MRI documentation whether these disorders preceded the SCL (as in 1°MD) or developed for the first time in life only after the SCL (as in 2°MD) and whether they continued currently. Subjects were then rediagnosed by DSM-IV criteria for MD and dysthymia from these data, with 100% agreement among the three DSM nosologies for subjects positive for MD and dysthymic disorder. Neurological and psychiatric evaluations and diagnostic formulations were conducted with the knowledge that subjects had some sort of SCL, but the evaluators were blind to the location of the lesions to prevent bias. Objective diagnoses were further ensured through the use of objective techniques such as the DIS, SCID, UPDRS, and Hoehn and Yahr staging.

Comparisons

After assessing the frequencies of 1°MD and 2°MD, we compared the period prevalence of 2°MD after SCLs to the life-prevalence of MD in age-, sex-, and race-matched external controls from the Epidemiologic Catchment Area (ECA) study.[40] To estimate comparability of frequency of 2°MD after SCLs with 2°MD in other subcortical disorders (such as PD and ID), we also compared the period prevalence of 2°MD after SCLs with the period prevalence of 2°MD identically nosologically defined and ascertained in 58 subjects with PD[8] and 28 subjects with ID[18] from other studies we are conducting after similar follow-up intervals (SCLs, 1–5-year follow-up; PD, 1–3-year follow-up; ID, 1–4-year follow-up). As a further point of reference to cortical disorders, we compared rates of 2°MD after SCLs with the rates of 2°MD in external controls with parietal[41] and left frontal[42] infarcts.

We then examined whether the rate of 2°MD was any more common after SCLs than the rate expected for the population at large (hypothesis 1). Nine subjects simultaneously met DSM-III, DSM-III-R, and DSM-IV criteria for MD occurring only after SCL onset (2°MD). An association between 2°MD and SCLs was tested by means of an odds ratio, and confidence intervals were computed by Cornfield's method with chi-square test, comparing the period prevalence for 2°MD after SCLs (period of time from lesion onset to time of study) with the life-prevalence of DSM-III MD in sex-, age-, and race-matched controls from ECA data.[40] We assumed the null hypothesis of no difference in prevalence between the two groups. Each SCL subject ($n = 45$) was matched to two ECA controls ($n = 90$), allowing DSM-III-based comparison. This constitutes a conservative comparison, potentially narrowing the difference between the groups, since life prevalence overestimates the ECA MD rate for the more limited time interval corresponding to SCL period prevalence. An accurate direct prevalence comparison of period to period is not possible because of the nature of ECA data.

We next determined whether depressive symptom severity was related to severity of parkinsonism (hypothesis 2) or dystonia (hypothesis 3) in the 45 SCL subjects. To test these relationships, we correlated Ham-D depression severity scores ($n = 42$) with UPDRS parkinsonism severity scores ($n = 45$) for hypothesis 2 and with DMS dystonia severity scores ($n = 23$) for hypothesis 3 among the 45 subjects with SCLs. We evaluated hypothesis 2 by linear regression analysis of Ham-D scores (dependent variable) against UPDRS scores (independent variable) among the 42 SCL subjects so rated. Similarly, hypothesis 3 was tested by linear regression analysis of Ham-D scores (dependent variable) against DMS scores (independent variable) among the 21 SCL subjects so rated. We assumed null hypotheses of no relation of Ham-D scores to UPDRS scores for hypothesis 2 and no relation of Ham-D scores to DMS scores for hypothesis 3.

Finally, we determined whether dystonia with geste occurs less frequently in subjects with 2°MD than in a group of subjects with SCLs with 1°MD who did not develop recurrent MD after SCLs despite their increased risk for MD relapse by reason of their previous history of 1°MD (hypothesis 4). Therefore, we compared the rates of geste in dystonia in the 9 2°MD subjects and the 8 1°MD subjects from our 45-subject sample with SCLs, using the one-tailed Fisher's exact test for small data. (Rate of geste equals the number of subjects with dystonia with geste divided by the number of subjects with dystonia with or without geste.) We assumed the directional null hypothesis of no lower rate of geste in dystonia in subjects with 2°MD. To estimate comparability between subjects with 2°MD and 1°MD (that is, whether the groups were too different to allow valid comparison), we compared demographic variables including age, sex, race, salary, social class, retirement status, education, marital status, duration of follow-up period, family history of depression, past medical history, and mental status exam. Mann-Whitney *U* and Fisher's exact tests were used for numerical and categorical data, respectively, correcting for multiple comparisons.

RESULTS

All 2°MD subjects were right-handed and had pallidothalamic SCLs (8 pallidal, 1 thalamic). Pallidal lesions

measured between 0.2 and 0.75 cm. Two were bilateral and 6 unilateral (2 right-sided and 4 left-sided). Pallidal lesions tended to be distributed in the posterior right and left pallida. The remaining subject with 2°MD had a 0.25-cm right anterior thalamic lesion. Both subjects with 2°DDNOS had nigrotegmental SCLs.

Post-SCL 2° depressive disorders occurred in 11 subjects (24.4%). These disorders simultaneously met DSM-III, DSM-III-R, and DSM-IV criteria and included: 9 (20.0%) with 2°MD; 0 (0%) with 2° dysthymic disorder; 2 (4.4%) with 2°DDNOS. Subjects with SCLs experienced 2°MD at a rate greater than ECA rates (6.7%), similar to subjects with ID (8 of 28, 28.6%) and PD (12 of 58, 20.7%) as well as external controls with parietal lobe infarction (28.6%),[41] yet less than external control rates for 2°MD after left frontal infarction (60.9%).[42]

1. *Hypothesis 1—Rate of 2°MD after SCLs vs. rate of MD in normative population:* Comparison with ECA data in which 6 of 90 had MD disclosed significantly more 2°MD with SCLs than expected (odds ratio 3.50; 95% CI 1.04–12.12; $\chi^2 = 4.134$, df = 1, one-tailed $P = 0.021$).
2. *Hypotheses 2 and 3—Association between movement disorder severity and depression severity:* Both UPDRS parkinsonism severity scores ($r = 0.524$, $F = 15.181$, one-tailed $P = 0.00018$) and DMS dystonia severity scores ($r = 0.478$, $F = 5.642$, one-tailed $P = 0.014$) were positively related to Ham-D depression severity scores.
3. *Hypothesis 4—Geste rates in 2°MD vs. in 1°MD with dystonia:* Geste antagonistique was less common in 2°MD (1 of 5 subjects with dystonia) than in SCL subjects with 1°MD (all 4 subjects with dystonia, Fisher's one-tailed exact test $P = 0.040$). Subjects with 1°MD did not differ from 2°MD controls with regard to demographic or social factors. Family history was compatible with MD in 5 of the 9 subjects with 2°MD (daughter with depression and suicide, husband with alcoholism; son with alcoholism and suicide; 2 brothers with depression and anxiety; brother with alcoholism; paternal aunt with depression and anxiety) and 2 of the 8 subjects with 1°MD (3 daughters with depression; sister with depression and suicide and brother with depression and anxiety).

DISCUSSION

Caveats

Several considerations limit the interpretation of the findings in this study. These include family histories compatible with depression in 5 subjects with 2°MD, refusal rate, small sample size, possible recall bias, and other limitations of follow-up studies. Family history is of particular importance because depression may result from genetic or other diatheses rather than SCL location. The 48.4% subject participation rate in the present study may lead to underestimation of depressive prevalence, since severely depressed subjects may have declined participation in the study because of depressive amotivation or social withdrawal. The death rate of 11.8% may include suicides, leading to further underestimation of depressive prevalence (although actual causes of death are unknown). In addition, the methodology employed may slightly underestimate DSM-IV depression prevalence. There were no significant differences between 1°MD and 2°MD subjects regarding demographic or social factors. Although this suggests that 1°MD controls constitute a suitable comparison group and that other factors did not differ between the two groups, these data do not preclude a nonbiological explanation for depression in our 2°MD subjects. Future studies may provide clearer results by controlling for these factors. Until further work is undertaken, the considerations discussed below must be considered tentative.

Findings

New findings from this study include the associations of 2°MD with pallidal SCLs, 2°DDNOS with nigral SCLs, depression severity with both parkinsonian and dystonic severity in subjects with focal SCLs, and the infrequency of geste in subjects with 2°MD and dystonia. Previously, left striatal (especially caudate) lesions have been associated with 2°MD,[23] in contrast to our pallidal findings obtained using different methodology.

Clinically, a high proportion of subjects with SCLs experienced 2°MD or its forme fruste (2°DDNOS). The rate of 2°MD after SCLs was comparable to rates of 2°MD in ID, PD, and parietal infarction, and about one-third as common as after left frontal infarcts. Given ECA prevalence data, at least several cases of dysthymia would be predicted in our sample if this disorder were at all positively related to SCLs in our study. (Limitations of sample size preclude testing for a negative relation or a protective effect of SCLs against dysthymia.) Hence, SCLs may lead to 2°MD but did not produce 2° dysthymia in our subjects.

Hypothesis 1: 2°MD occurred more commonly after SCLs than expected by chance alone compared with age-, sex-, and race-matched normative ECA controls. This statistical association suggests that 2°MD may be attributable to SCLs.

Hypotheses 2–4: Among SCL subjects with current de-

pression (including 2°MD, 2°DDNOS, or subsyndromal depressive symptoms), those with more severe Ham-D depression scores had greater parkinsonism (hypothesis 2) and dystonia (hypothesis 3) severity scores. Subjects with 2°MD and dystonia usually lacked control over their dystonia due to an absence of geste antagonistique (hypothesis 4) compared with a greater prevalence of geste in 1°MD controls, although there were no discernible differences between these two groups along psychosocial variables. These findings are consistent with suggestions in the literature that PD disability leads to depression[26] and the view that depression in dystonia may be a consequence of poor symptom control.[27] Thus, psychosocial stress related to these disabilities after SCLs may contribute to depression.

Biological Considerations

Another possible explanation is that the biology of the SCLs precipitates depression. The frequency of 2°MD after pallidothalamic SCLs was roughly similar to rates in other subcortical disorders known to be associated with increased rates of depression, namely PD[1–12] and ID.[13–19] These results are also consistent with findings of subcortical pathology associated with depression in elderly subjects.[43–46] A biological rather than a psychosocial explanation of depressive symptoms in our SCL subjects is also suggested by the positive relation of depression score severity to both parkinsonism and dystonia score severity in our SCL subjects. Menza and Mark[47] previously found a relationship between PD disability and depression. Nevertheless, in previous investigations we have found poorer correlations of Ham-D scores with parkinsonian (Hoehn and Yahr stage, $r = 0.346, F = 5.446, P = 0.0247$) and dystonic (DS, $r = 0.257$, $F = 1.408$, $P = 0.249$) measures of disability than the correlations found with the UPDRS and DMS symptom scales in the present study. We might expect stronger correlations with disability scales than with symptom scores if the psychosocial effects of disease disability produced the depression. Thus, a subcortical biological explanation of depression may apply in our subjects.

How might the biology of these SCLs relate to depression in our subjects? Interruption of pallidal[20,48] and thalamic[49] subcortical circuits[22,50,51] disturbs frontal lobe function through thalamocortical neurons and may produce the 2°MD we observed after SCLs (Figure 1). These subcortical structures strongly influence frontal lobe functioning.[52,53] It logically follows that disruption of these structures could lead to frontal dysfunction such as that seen in 1°MD[54] and 2°MD,[25] as we have extensively explained and referenced elsewhere.[20,49] This reasoning seems to reflect clinical reality, since basal ganglia lesions lead to mental disturbances associated with frontal dysfunction such as delirium[55,56] and dementia (as in Huntington's disease). More to the point, lesions of the pallidum have been associated with both 2°MD[20] and psychic akinesia,[57] a condition resembling a subset of features of MD. Further, diseases that destroy the pallidum (Fahr's syndrome,[20,21] carbon monoxide poisoning,[58] Wilson's disease[59]) or lead to inhibition[53] of the external pallidal segment (PD[1–12]) are associated with 2°MD. Physiologically, destruction or inhibition of the external pallidum disinhibits the internal pallidum.[52] This increases internal pallidal inhibition on parvocellular mediodorsal and other thalamic nuclei and leads to reduced thalamic activation of the frontal lobe.[20,48,49] This physiological result comports well with the strong association of left frontal lesions with 2°MD, which is independent of handedness or cerebral dominance,[42] and with the metabolic hypofrontality seen in 1°MD and 2°MD referred to above.

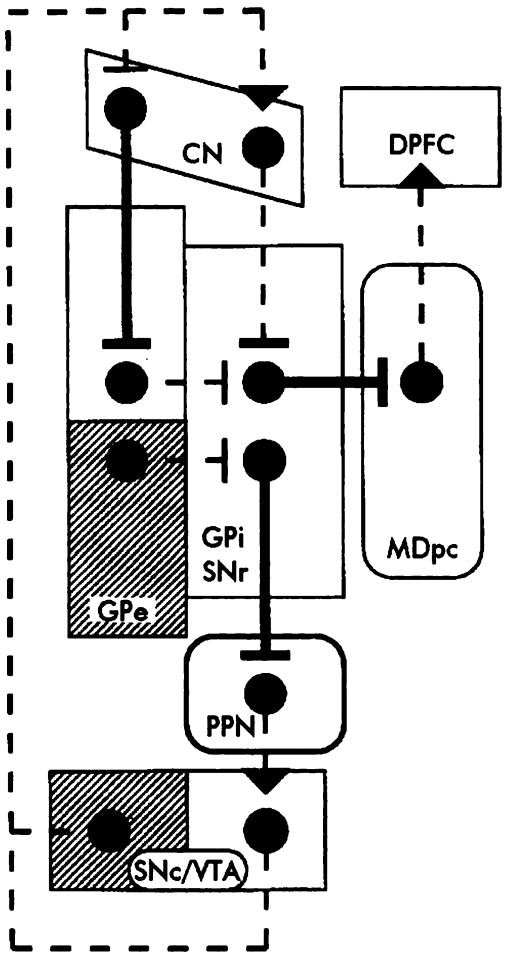
Both subjects with forme fruste expression of 2°MD (2°DDNOS) had nigrotegmental lesions and parkinsonism (1 with dystonia without geste, 1 without dystonia) without visible lesions of pallidothalamocortical systems, suggesting that dopaminergic failure without pallidothalamocortical compromise may lead to limited-symptom depressive forme fruste presentations.[1,24] Indeed, across our SCL subject sample, Ham-D depressive severity scores increased as UPDRS parkinsonian severity scores increased. This finding is in concert with that of Starkstein et al.,[60] who found more severe cardinal parkinsonian signs in idiopathic PD with late-onset depression. Both parkinsonism and some forms of dystonia are well known to relate to reduced nigral dopamine function. In light of this association, it is of interest that Ham-D scores in our SCL subjects also correlated positively with DMS dystonia severity scores. Brown and Gershon[24] recently reviewed the relationship between diminished dopamine and depression. Weinberger and Berman[61] suggested the importance of dopamine in frontal lobe hypometabolism in depression. More specifically, Fibiger[62] and Cummings[1] have detailed the importance of tegmental mesocortical dopamine depletion as a potential explanation of anhedonia, amotivation, and apathy in PD 2°MD. Further, electroconvulsive therapy improves MD as well as parkinsonian symptoms[63–65] and some forms of dystonia[65,67] (including parkinsonism-dystonia[66]), perhaps through restoration of dopaminergic function.[66] Consequently, mesocortical dopaminergic dysfunction may relate to depressive symptoms across SCL subjects, particularly those with 2°DDNOS. In addition, reduced nigrostriatal dopaminergic transmission reduces D_2 dopamine receptor–mediated inhibition of the striatum (see Figure

1). Disinhibition of the striatum increases striatal inhibition of the external pallidum,[53] producing a physiological effect similar to a pallidal lesion. Pallidal lesions in 2°MD may disrupt dopaminergic and other neurotransmitter functioning through pallidal connections with the pedunculopontine cholinergic nucleus, which, in turn, influences serotonin (raphe nuclei), norepinephrine (locus ceruleus), dopamine (ventral tegmental area), and reticular and limbic systems.[67–69]

An interaction of several pathophysiologies may relate to 2°MD. In addition to frontal lobe compromise through pallidothalamofrontal, ventral tegmental mesocortical, and nigrotegmentobasal ganglia pathways, subcortical parietofrontal pathways may also play a role. Geste in dystonia seems to require the integration of parietal lobe somatosensory circuit information to regulate frontal lobe motor and premotor circuit dystonic activity, since sensory input can attenuate dystonia in patients with geste.[32] The absence of dystonic geste in traumatic dystonia[70] and the rarity of geste in our subjects with 2°MD may suggest a breakdown in interaction between parietal and frontal lobes in these conditions. Disrupted subcortical mediation of parietal-frontal interaction, perhaps through the posterior pallidum, may eventuate in 2°MD and may also account for the cortical metabolism gradients observed in primary[54] and secondary depressions[25] as well as the absence[71] of parietal serotonin upregulation in depression after frontal infarcts.[72] Both parietal and frontal strokes are associated with depression.[73] Further, several studies have found paired parietal and frontal deficits in behavioral testing,[74] metabolism,[75] and blood flow[76,77] in depression. Thus, SCLs disturbing pallidothalamocortical circuits, dopamine neurons, other neurotransmitters, or physiological connections between cortical areas may relate to 2°MD through a pathophysiological impact on the left frontal cortex.

Clinically, selection of 1°MD subjects as a control group not only allows identification of factors associated with 2°MD but may also elucidate factors that, when absent, might protect against the development of depression in subjects at risk for depression after SCLs. Subjects with 1°MD are at risk for depressive recurrence because they had previous depressive episodes prior to SCLs and suffer the same stressor (SCLs) as subjects with 2°MD. Consequently, the difference in geste rate between 1°MD and 2°MD may indicate that an absence of geste in subjects with dystonia after SCLs may predispose to 2°MD. In subjects with dystonia after SCLs, the presence of geste might potentially protect against the evolution of MD following SCLs in subjects with a history of 1°MD.

FIGURE 1. Basal ganglia–thalamofrontal mood circuits. SNc/VTA lesions lead to reduced striatal inhibition on GPi/SNr as well as increased striatal inhibition on intact GPe, which also disinhibits GPi/SNr, increasing GPi/SNr inhibition on MDpc and thus reducing frontal stimulation. GPe lesions disinhibit GPi/SNr, producing the same effect. Disinhibition of GPi/SNr further inhibits PPN stimulation of SNc/VTA, leading to reduced dopamine supply to the striatum, as in SNc/VTA lesions. Reduced DPFC stimulation may lead to depression.



CN	caudate nucleus
DPFC	dorsal prefrontal cortex
GPe	external globus pallidus
GPi	internal globus pallidus
MDpc	parvocellular mediodorsal thalamic nucleus
PPN	pedunculopontine nucleus
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
VTA	ventral tegmental area
///	lesion
⊥	inhibitory neuronal connection
→	excitatory neuronal connection
—	increased tone
- - -	decreased tone

Clinical Considerations

Patients with pallidothalamic SCLs, especially when accompanied by dystonia without geste, may be at risk for 2°MD, whereas nigral SCLs may carry a risk for 2°DDNOS. Patients with SCLs and severe symptomatic parkinsonism or dystonia may also be at risk for various depressive conditions. Depression may evolve late after these insults[49,78] as neurotransmitters and their receptors change over time subsequent to a lesion.[72] This possibility underscores the clinical importance of monitoring patients with SCLs closely and carefully for depression over a period of several years subsequent to the lesion. In light of the occasional presentation of depression as 2°MD forme fruste (2°DDNOS), a thorough evaluation of all signs of MD should be undertaken to pick up subtle cases exhibiting only partial syndrome expression. However, the limitations of this study necessitate caution in drawing conclusions from these small data and indicate the need for further research into depressive disorders after SCLs.

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