Lesion Location and Poststroke Depression
Systematic Review of the Methodological Limitations in the Literature
Sanjit K. Bhogal, BA(Hon); Robert Teasell, MD; Norine Foley, BASc; Mark Speechley, PhD

Background—It has been hypothesized that poststroke depression (PSD) results from left hemisphere lesions. However, attempts to systematically review the data investigating lesion location and PSD have yielded conflicting results. We sought to investigate the methodological differences across the literature studying the relationship between lesion location and PSD.

Summary of Review—A MEDLINE literature search to retrieve articles investigating the association between PSD and lesion location was performed. Information sought included source population of samples, definition of depression, standardized measurement of stroke and depression, blinding, time since stroke onset, and study design. Odds ratios (ORs) and 95% CIs were calculated with the use of Review Manager and MetaView statistical software. Twenty-six original articles were reviewed. Much of the heterogeneity across studies reflected differences in methodology. The direction of association between left hemisphere lesion location and PSD varied depending on whether patients were sampled as inpatients (OR, 1.36; 95% CI, 1.05 to 1.76) or from the community (OR, 0.60; 95% CI, 0.39 to 0.92). Change in the direction of association was also observed across assessment interval from the acute stroke (OR, 2.14; 95% CI, 1.50 to 3.04) to the chronic stroke (OR, 0.53; 95% CI, 0.30 to 0.93) phase. Differences in the measurement of depression, study design, and presentations of results also may have contributed to the heterogeneity of the findings.

Conclusions—Several key initiatives should be addressed before future research is undertaken, including the development of a comprehensive measure of PSD, optimal poststroke assessment intervals, and determination of a representative population reference. (Stroke. 2004;35:794-802.)

Key Words: brain diseases □ cerebrovascular accident □ depression □ methods □ review literature

Depression is a common sequela of stroke. The prevalence of clinical depression varies from 20% to 50% among inpatients during the acute and subacute phases of recovery.1 Poststroke depression (PSD) has been reported to negatively affect functional and cognitive recovery2-5 and is associated with social withdrawal after stroke6,7 as well as increased mortality.8

Two theories of PSD have been espoused. The first states that depression after stroke or after brain injury is a psychological reaction to the clinical consequences of stroke. The second suggests that depression arises as a consequence of the specific brain lesion and presumably subsequent changes in neurotransmitters. Accordingly, Folstein et al9 observed that stroke patients suffered more from depression than equally physically impaired orthopedic patients, thereby suggesting that the brain lesion itself could influence mood. Furthermore, differences in emotional reactions depending on hemisphere of the infarct suggested an organic basis of PSD.10

The association between the location of brain lesion as a result of stroke and PSD has been the topic of much research. However, this complex association is not well understood11 despite the large number of studies that have examined the association. Recent attempts to systematically review studies of lesion location and PSD have not served to clarify this association. Pooling previous results, Robinson12 identified specific relationships between the locations of brain injury and the character and severity of poststroke mood disturbances. Robinson12 suggested that left anterior cerebral lesions were associated with significantly higher depression scores than left posterior lesions. Diagnosable depressive disorders were found in approximately 70% of stroke patients with left frontal brain injuries. Robinson12 estimated that only 15% of the variance in depression could be explained by the severity of intellectual impairment, physical impairment, quality of social support, or age, whereas the site of the lesion explained 50% of the variance.

In contrast, a systematic review by Carson et al13 found that when data from 34 primary studies were pooled, lesion location was not associated with depression. The pooled relative risk of depression after a left hemisphere stroke,
compared with a right hemisphere stroke, was 0.93 (95% CI, 0.83 to 1.62). The authors noted that restricting the analyses to “higher-quality” studies or major depressive disorders did not affect their findings. Furthermore, the results were not affected by stratification of time between stroke and the assessment of depression. Thus, this systematic review offered no support for the hypothesis that the risk of depression after stroke was influenced by lesion location.

A review conducted 2 years earlier did not yield definitive conclusion concerning stroke lesion location and the risk of depression. Singh et al systematically selected 26 original articles that examined lesion location and PSD, of which 13 satisfied inclusion criteria. The authors noted that all of the studies reviewed were methodologically flawed and were not comparable with respect to sample, timing, and analysis of CT scan and psychiatric evaluation. As a result, Singh et al did not believe that they could proceed with a formal evaluation.

The inconsistent results among these 3 reviews (1 found an association, 1 found no association, and 1 believed that the studies could not be compared) indicate that there are methodological problems in the PSD literature. There is a lack of uniformity in the definition of stroke given the various classifications of stroke that are used (eg, definition based on clinical consideration versus category of stroke). When stroke diagnostic criteria are unclear, data collection and selection of appropriate samples for research are also unclear. Likewise, there is a lack of uniformity in the definition and measurement of depression. To further complicate the issue, it is often difficult to differentiate endogenous depression from an adjustment reaction to losses suffered after the stroke event. Because of this last point, it is difficult to separately test the 2 competing theories because the assessment of the outcome will be confounded within and between studies.

Given the inconsistent results across the 3 aforementioned reviews and the methodological concerns regarding research in PSD, in this article we review and critique the research methodology used in studies investigating the relationship between stroke lesion location and depression. Although Carson et al examined the relative risk of developing PSD according to time since stroke onset and source of patients, this article provides a more thorough methodological review of the literature in an attempt to explain the heterogeneity of results across the literature. In addition, key research initiatives within the area of PSD are proposed. Areas of interest include the sample population source, definitions of stroke and depression, imaging used, timing of diagnosis, and statistical analysis.

Methods

Study Identification and Selection
Two MEDLINE literature searches (via PubMed) were used to identify all studies from January 1970 to March 2003 that investigated the association between stroke lesion location and depression. Search limits included English, human, middle age: 45+. The first search included the key words depression, cerebrovascular accident or stroke, computerized tomography or CT scan, and post stroke and the combined exploded key words depression AND cerebrovascular accident OR stroke AND computerized tomography OR CT scan AND post stroke. The second search included the key words depression, cerebrovascular accident or stroke, and computerized tomography or CT scan and the combined exploded key words depression AND cerebrovascular accident OR stroke AND computerized tomography OR CT scan. Articles identified in the MEDLINE searches were included if the purpose was to study the association between stroke lesion and the development of PSD. Studies were limited to stroke survivors and excluded studies that included nonstroke patients.

Eleven articles were retrieved from the first search, of which 1 was a review article and 5 met inclusion criteria. The second search yielded 34 articles, of which 2 were review articles, 3 were duplicates from the previous search, and 18 met inclusion criteria. Studies cited in the retrieved articles but not identified through the MEDLINE literature search were sought, bringing the total number of primary articles retrieved to 38.

Data Abstraction
A single reviewer extracted data from the selected studies onto a data abstraction form. Information sought included sample population, definition of stroke, definition of depression, standardized measurement of stroke, standardized measurement of depression, lesion volume and lesion localization method, blind assessment of depression to CT scan and vice versa, timing, and final conclusions.

Statistical Analysis
For articles that did not report odds ratios (ORs) and/or CIs, frequency of patients with and without depression and site affected were recorded from the articles; the Peto OR and 95% CI were calculated with the use of Review Manager and MetaView, a statistical software package available from the Cochrane Collaboration Group. Differences in the frequency of depressed and nondepressed patients between left and right hemisphere strokes were assessed by the chi-square statistic with Yates correction with the use of Statcalc, a statistical software package available through the Centers for Disease Control. Fisher’s exact test was used when observed cell counts were <5. Statistical significance was set at the 0.05 level.

Results
A total of 38 articles were retrieved. Seven articles were excluded because they did not meet inclusion criteria. In 2 instances, multiple articles reported different analyses performed on a single group of patients (References 1, 7, 24, 25 and References 26, 27). In the end, 26 original reports were included in the review (Table). Given that many studies did not provide ORs and/or CIs, the present article calculated the OR of developing PSD for a left hemisphere stroke (Figure 1). ORs and/or CIs could not be calculated for all studies because of insufficient detail in the reports of the findings. One study did not provide the number of nondepressed patients who had suffered either a left or right hemisphere stroke. Five studies did not provide frequency counts of the number of depressed
and nondepressed patients with either left or right hemisphere strokes.10,32,33,38,47

As shown in Figure 1, the 95% CIs for individual studies were wide, and the test of heterogeneity was highly significant ($\chi^2 = 75.45$, $P < 0.00001$), indicating substantial variation in OR among studies. As noted earlier, much of this variation is believed to reflect the methodological differences of the literature. A review of the main methodological differences that may contribute to heterogeneity across studies follows.

Source Populations and Study Samples
The source of patients was observed to vary across studies. Patients were selected from 2 main sources: hospital-based patients† or community-based patients.22,23,29,34,35,42,47 The population base of the study sample has been proposed by some investigators15,48 to influence the outcome of the association between lesion location and PSD. When studies are examined according to population source, 2 trends emerged (Figure 2). Studies of hospital inpatients significantly favored depression occurring after left hemisphere stroke (OR, 1.36; 95% CI, 1.05 to 1.76), whereas studies of community-based samples were observed to significantly favor depression after a right hemisphere stroke (OR, 0.60; 95% CI, 0.39 to 0.92).

An interesting finding was that the test of heterogeneity was significant across hospital inpatient studies ($\chi^2 = 62.84$, $P < 0.00001$) but not across community-based studies ($\chi^2 = 1.62$, $P < 0.81$). The significant heterogeneity across hospital inpatient studies may reflect differences in the composition of the study samples due to different healthcare practices. For example, in Sweden 90% of all stroke patients are admitted to the hospital; therefore, a hospital-based study of stroke patients in this region is representative of most stroke patients.36 However, in some regions fewer than half of stroke patients are admitted at the time of acute episode.35

Patients characteristics also differed among studies. Several samples were predominantly characterized by inner city residence, low income, and black ethnicity, with approximately one half possessing less than a grade 9 education.7,30,31,41,46 On the other hand, the patients of Singh et al14 were predominantly middle-class suburban residents, and 66% of the Sharpe et al34 sample was white.

Other inconsistencies in sample composition due to inclusion criteria were also noted. Lipsey et al28 recorded patients with a history of alcohol abuse and noted that more of these patients were in the left hemisphere group than the right hemisphere group (50% versus 17%). Similarly, inclusion of patients with aphasia resulted in a higher percentage of patients with communication disorders in the left hemisphere.

### Articles Investigating Lesion Location and Poststroke Depression (n=25)

<table>
<thead>
<tr>
<th>Article</th>
<th>Prevalence of PSD, %</th>
<th>Association</th>
<th>Onset Since Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipsey et al28</td>
<td>34</td>
<td>Left hemisphere</td>
<td>Within 2 weeks</td>
</tr>
<tr>
<td>Robinson et al10,24; Parikh et al35</td>
<td>47</td>
<td>Left hemisphere</td>
<td>30–60 days</td>
</tr>
<tr>
<td>Sinyor et al30</td>
<td>23</td>
<td>Association changes over time</td>
<td>~55 days</td>
</tr>
<tr>
<td>Collin et al29</td>
<td>30</td>
<td>No association</td>
<td>Undefined</td>
</tr>
<tr>
<td>Starkstein et al30</td>
<td>31</td>
<td>Left hemisphere</td>
<td>&lt;2 months</td>
</tr>
<tr>
<td>Starkstein et al31</td>
<td>42</td>
<td>Left basal ganglia</td>
<td>7–18 days</td>
</tr>
<tr>
<td>Starkstein et al32</td>
<td>Not given</td>
<td>Association changes over time</td>
<td>35 days</td>
</tr>
<tr>
<td>Dam et al32</td>
<td>30</td>
<td>Right hemisphere</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td>Sharpe et al34</td>
<td>18</td>
<td>No association</td>
<td>4–5 days</td>
</tr>
<tr>
<td>House et al35</td>
<td>20</td>
<td>No association</td>
<td>1 month</td>
</tr>
<tr>
<td>Astrom et al38</td>
<td>25</td>
<td>Association changes over time</td>
<td>3–5 years</td>
</tr>
<tr>
<td>Agrell et al37</td>
<td>29</td>
<td>No association</td>
<td>Undefined</td>
</tr>
<tr>
<td>Andersen et al22</td>
<td>Not given</td>
<td>No association</td>
<td>Within 7 days</td>
</tr>
<tr>
<td>Burvill et al33</td>
<td>Not given</td>
<td>No association</td>
<td>4 months</td>
</tr>
<tr>
<td>Jacoboni et al38</td>
<td>36</td>
<td>Association changes over time</td>
<td>7 days</td>
</tr>
<tr>
<td>Herrmann et al39</td>
<td>22</td>
<td>Left basal ganglia</td>
<td>Within 2 months</td>
</tr>
<tr>
<td>Morris et al40</td>
<td>24</td>
<td>Left basal ganglia</td>
<td>Within 1 month</td>
</tr>
<tr>
<td>Morris et al41</td>
<td>34</td>
<td>Left hemisphere</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Angeleri et al42</td>
<td>29.7</td>
<td>No association</td>
<td>Within 10 days</td>
</tr>
<tr>
<td>Gainotti et al28,27</td>
<td>42.5</td>
<td>No association</td>
<td>37.5 months on average</td>
</tr>
<tr>
<td>Nagaraja et al43</td>
<td>24</td>
<td>No association</td>
<td>2 weeks and 6 months</td>
</tr>
<tr>
<td>Pohjasaava et al44</td>
<td>20</td>
<td>No association</td>
<td>Within 3 weeks</td>
</tr>
<tr>
<td>MacHale et al45</td>
<td>50</td>
<td>Right hemisphere</td>
<td>6 months</td>
</tr>
<tr>
<td>Shimoda and Robinson46</td>
<td>Not given</td>
<td>Association changes over time</td>
<td>3 months</td>
</tr>
<tr>
<td>Sato et al47</td>
<td>52</td>
<td>Association changes over time</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Singh et al48</td>
<td>36</td>
<td>Association changes over time</td>
<td>3 months</td>
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†References 7, 10, 26, 28, 30–33, 36–41, 44–46, 48.
stroke group than in the right hemisphere stroke group in 2 studies.39,44 In addition, 86% of the left hemisphere patients in the study of Shimoda and Robinson46 had a family history of psychiatric disorder. Alcohol abuse, family history of a psychiatric disorder, and aphasia can increase the risk of developing depression. The fact that these factors were overrepresented in 1 group (ie, the left hemisphere stroke group) may partly explain why a difference in the frequency of depression between the 2 hemisphere groups was found in these articles.

Definition, Diagnosis, and Standard Measurements of Depression

Assessment of Depression

The timing and location of the assessment of depression were well described in most articles. Most of the studies conducted on hospital-based patients explicitly stated that patients were interviewed for depressive symptoms in a private room, between 11 AM and 2 PM, to minimize diurnal mood variation.7,26,28,30–32,37,38 Several studies assessed patients in their residence, including their own homes or nursing homes.22,23,34,35,42 Collin et al29 mailed out a questionnaire regarding depressive symptoms to stroke patients living in the community.

The most common measures used to assess the severity of depression were the Hamilton Depression Rating Scale (HDRS) and the Zung Self Report Depression Questionnaire.14,26,28,30–32,37,38 Lipsey et al38 calculated an overall depression score based on the Zung questionnaire and the HDRS, whereas Dam et al13 used the HDRS in conjunction with the Beck Depression Inventory (BDI). Other measures used to assess the degree of depression were the BDI alone,15,18 the Beck Hopelessness Scale,10 the Hopkins Symptom Check-
specificity and poor predictive values because of their inclusion of somatic symptoms.

There has been considerable debate regarding the use of self-report measures to diagnose and measure depression, given the known incongruity between DSM-III diagnostic criteria and psychometric measures.51 Dam et al33 observed significantly higher degrees of depression in patients with right hemisphere stroke when measured by the HDRS; however, this difference disappeared when the BDI was used. Dam et al33 suggested that this was caused by indifference to the symptoms that are often seen in patients with right hemisphere lesions. This neglect would be more pronounced in self-rating than in an interviewer-scored scale. Gordon et al51 noted that the HDRS alone was more congruent with the DSM-III than were self-report measures. The combination of self-report measures (eg, the Zung scale) with the HDRS resulted in a discrepancy with DSM-III diagnosis of depression.51 It has been suggested that the discrepancies resulting from sole use of self-report measures were due to underreporting of depressive symptomology compared with observer rating.51 Gordon et al51 interpreted the findings to suggest that either patients tend to minimize the severity of their mood disorders or examiners are sensitive to patients’ behaviors.

Timing of First Interview After Stroke
Timing of first interview for depressive symptoms ranged from the acute period7,22,30–32,36–41 to the subacute phase of stroke rehabilitation23,35,44,45,48 to the chronic phase.34,42 One study was noted to have staggered assessment times between the acute and chronic stages of stroke.26

The time of assessment since stroke onset can potentially influence study outcome. Patients interviewed during the subacute phase may still be adjusting to their stroke experience, and depression in these patients may reflect this transition stage. In fact, the highest rates of depression were noted in patients assessed within the first 28 days of stroke (Table). When we examined studies that assessed depression within the first 28 days of stroke, a significant association between left hemisphere stroke and PSD was demonstrated (OR, 2.14; 95% CI, 1.50 to 3.04). However, studies that assessed depression between 1 and 4 months observed that the association began to favor development of PSD after right hemisphere stroke (OR, 0.93; 95% CI, 0.66 to 1.32), with a significant association between right hemisphere stroke and PSD at 6 months (OR, 0.53; 95% CI, 0.30 to 0.93) (Figure 3). It is possible that the difference in association across the 3 time intervals reflects the degree of transient mood changes related to the stroke event itself. Shimoda and Robinson46 suggested that impairments such as social isolation or visual perceptual disorders associated with right hemisphere strokes may play a role in the etiology of depression in the chronic phases of stroke. Andersen et al22 suggested that this trend may be reflective of the neuropsychological changes that may
follow hemisphere strokes: catastrophic reaction with left hemisphere strokes and denial and/or neglect or aprosody with right hemisphere lesions. Accordingly, several follow-up studies have suggested that PSD occurring in the chronic phase may have a different mechanism than acute or subacute PSD. 10,32,36,38,46–48

Research Design: Cohort Versus Case-Control Study

Of the 25 studies reviewed, only 13 studies stated explicitly how groups were assigned. Seven studies grouped patients according to lesion characteristics, thereby using a cohort design. 1,22,30,31,36,41,45,48 Three studies 33,36,40 used a case-control design in which patients were sampled according to depressive symptoms. Gainotti et al 26 and Sato et al 47 used a cross-sectional design. Knowledge of whether patients were grouped according to lesion location or depression status is important to determine the potential bias that may affect a study. For example, if patients were grouped according to lesion characteristics, then the findings might be biased as a result of patients with lesions in certain stroke locations being probed more for depressive symptoms or lack thereof. Grouping patients according to their depressive symptoms runs the risk that the radiologist reading the CT scan may be biased to look for signs of lesions in one hemisphere or another.

The majority of studies ensured that the neurological evaluators were blinded to the findings on psychopathological examination and that CT scans were read by an investigator who was blinded to all clinical findings. 26 Six studies made no specific mention regarding blinding of assessors. 28,33,37,40,42,44 Although blinding of both the radiologist and psychiatrist helps to reduce interview and detection bias, in the case of the psychiatrist, the clinical presentation (eg, side of hemiparesis) of a stroke patient provides clues regarding the location of the stroke. A solution would be to ensure that all assessors involved are unaware of the study’s hypotheses and prediction. Unfortunately, none of the reviewed studies indicated whether the assessors were unaware of the purpose of the study.

Presentation of Results

Level of Statistical Significance

Eight of the studies indicated that all analyses were performed as 2-tailed tests at the 0.05 level. 34–37,39,42,45,48 The importance of stating whether a test was performed as a 1-tailed versus 2-tailed test was highlighted by the results of Starkstein et al, 30 who did not state whether they tested significance at a 1-tailed or 2-tailed level. A reanalysis of their findings using a 1-tailed test demonstrated a significant association (Yates $=2.78, P=0.044$), a result very similar to that presented by Starkstein et al. 30 However, with the

References 7, 22, 23, 26, 30–32, 34, 35, 38, 45, 46, 48.
2-tailed test the probability value becomes 0.09, which is nonsignificant at the 0.05 level. Therefore, their alternate hypothesis of unequal frequency of either major or minor depression on the basis of left or right hemisphere lesion location was not sustained according to a 2-tailed test. One other study performed a 1-tailed test of significance.28

**Adjustment for Multiple Comparisons**

Another statistical error noted was the effect of multiple comparisons on the α level. Morris et al41 found no significant association in the frequency of depression between right and left hemisphere strokes. The authors then stratified on the basis of size of lesion and performed multiple tests without correcting for the number of comparisons. Robinson et al7 also performed multiple tests on their study sample without correcting their level of significance. Only 2 studies14,42 used a Bonferroni-adjusted α level for multiple testing, and neither study found a significant association between lesion location and PSD.

**Severity Versus Frequency**

A common trend noted in the results was the tendency to interchange the outcomes of severity of depression and frequency of depression. Robinson et al7 indicated that left hemisphere stroke patients had greater depression scores than right hemisphere stroke patients as indicated on psychometric scales, whereas the difference in frequency was not reported. Similarly, Dam et al43 measured the severity of depression but not the frequency of depression. Herrmann et al39 and Angeleri et al42 also stated that the severity of depression was greater in left versus right hemisphere lesions, but when frequency of depression was examined, there was no difference between lesions involving the left or right hemisphere.

**Use of Regression Models**

Regression analysis was used in 3 studies. MacHale et al45 used stepwise regression to determine the predictive power of lesion location on the development of PSD. Similarly, Sato et al47 performed bivariate analyses with dummy variables used to model lesion site, and the regression coefficient for each variable was determined via stepwise regression. Singh et al48 used multiple linear rather than logistic regression modeling because dichotomization of the depression variables was arbitrary.

Inappropriate analysis and presentation of results contribute to the differences in the literature. Use of inappropriate levels of significance misleads the readers. Moreover, the interchange use of severity of depression and frequency of depression makes interpretation of results difficult. Finally, the general absence of multiple regression models in the literature suggests that the effects of confounding variables were not removed from summary estimates of association between lesion location and PSD.

**Discussion**

There were methodological differences across the PSD literature. These differences contribute to the discrepant findings in the association between lesion location and PSD. Much of the heterogeneity noted across the studies appeared to be a function of the population source. Left hemisphere lesion location appeared to contribute to the development of PSD in hospital inpatient population studies. Right hemisphere lesion location appeared to contribute to the development of PSD in community-based population studies. Differences in time since stroke onset and the lack of a standard tool to assess PSD also appeared to contribute to the heterogeneity of findings. Furthermore, the inappropriate presentation of statistical analysis added to the limitations of the literature.

Even if the site and size of the brain lesion in stroke were significantly correlated with depression, it is difficult to determine whether depression is due to the clinical consequences of stroke or due to neurophysiological changes that may lead to depression. At present, it is not known whether certain types or degrees of neurocognitive impairment and disability are associated with more or less depression.

The association of PSD and left hemisphere damage, although compelling when the work of 1 group (the Johns Hopkins group) is considered, has not been adequately or consistently confirmed.15 The association between the site of the stroke lesion and the likelihood of developing depression independent of the clinical consequences remains unproved. The authors decided to focus only on hemisphere lesion location for simplicity since the methodological differences that arose from hemisphere CT location were great. As a result, the authors recognize that a limitation of this review is that other lesion variables, such as anterior-posterior lesion location, were not examined. It is possible that these variables may also play a role in the development of PSD.

Before further research in this area is conducted, several key initiatives should first be undertaken. These include the following: development of an appropriate and standardized measure of depression; identification of a representative population source for research purposes; use of optimal time since stroke onset to interview for PSD; and creation of more comprehensive predictive causal models of PSD (as opposed to investigation of lesion characteristics alone as a predictor of PSD).

**Development of an Appropriate and Standardized Measure of Depression**

A measure of depression that is best suited for the stroke population is required. Such a measure would take into account the functional, cognitive, and language impairments that often accompany stroke. Furthermore, a measure of depression for the stroke population must be sensitive to some of the potential vegetative symptoms of the stroke itself (psychomotor retardation, fatigue, and sleep and appetite disturbances) that most conventional scales classify as depressive symptoms.

**Identification of a Representative Population Source**

Given that the population source of a study can influence results, the choice of entirely hospital-based samples or entirely community-based samples will systematically skew results. Accordingly, researchers should work together in conducting large-scale studies that involve follow-up of all stroke patients coming to emergency departments for treatment, regardless of whether they were admitted to the hospital or sent back to the community for treatment.
Optimal Time After Stroke Onset to Interview for PSD

Several authors have suggested that PSD over the long term may have a different mechanism than acute or subacute PSD with left-sided stroke and denial and/or neglect or aprosody with right-sided lesions. Therefore, a prospective cohort design would be best suited for studying the relationship between lesion location and PSD. As patients are followed, data regarding their recovery and present state should be kept current.

Creation of Predictive Causal Models of PSD

Many of the studies reviewed investigated only the association between lesion location and PSD. Further multifactorial approaches were taken by only 3 studies. Given that depression in the general population is multicausal, the study of depression in the stroke population should be viewed as such. On the basis of the research thus far, PSD should be studied in terms of lesion location, functional impairment, social dependence, intellectual impairment, and stroke onset. Like other fields of psychiatry and psychology, the study of PSD is riddled with methodological differences. An analysis of these differences can be used to guide future research. One such direction is the development of a depression measure for the stroke population. Not only would such a measure allow for accurate and reliable diagnosis of stroke for research purposes, but it might also help clinicians to distinguish true clinical depression from reactive adaptation in their patients. In addition, the realization that depressive symptoms manifest themselves differently during stroke recovery (acute versus subacute versus chronic) and also across populations (hospital inpatient versus community) allows researchers and clinicians to approach the diagnosis and treatment of depression accordingly. Finally, use of a multifactorial approach would allow researchers to study several means by which different stroke survivors can develop PSD. Such an approach can be used to explain the variability in the frequency and severity of PSD across populations and time. In addition, understanding PSD in terms of causal complexes would allow clinicians to monitor patients at risk of developing PSD.

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References

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