RELATIONSHIP BETWEEN POST-STROKE DEPRESSION AND LESION LOCATION: A META-ANALYSIS

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Our understanding of the relationship between the neuroanatomic loci of brain damage and the incidence of post-stroke depression (PSD) is not complete. Many studies have investigated this relationship and the evidence is conflicting. With the purpose of gaining a consistent, strong, and credible conclusion on the relationship between PSD and the loci of brain damage, a meta-analysis was used in this study to systematically reanalyze the findings of related studies and to investigate the sources of heterogeneity among study results. The key words "stroke or cerebrovascular" and "depression or mood or affective" were entered into the MEDLINE, PsycINFO, and EMBASE databases to search for relevant studies. The references cited in the studies found were also used to locate additional studies. For each eligible study, the important study characteristics were recorded, and the effect sizes of the relationship between PSD and lesion location were computed. Furthermore, we conducted subgroup analyses to explore the heterogeneity among study results. A total of 3,668 patients participating in 52 studies were included in this meta-analysis. There was a weak relationship between PSD and right hemisphere lesion. The major sources of heterogeneous study results included systematic exclusion of patients with language dysfunction and use of different assessors and instruments for diagnosing depression. Future efforts should aim to enhance standards for reporting studies, improve assessment tools for assessing depression of aphasic patients, and adopt appropriate study methodologies for investigating the relationship between PSD and lesion location.

Key Words: post-stroke depression, lesion location, meta-analysis
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The hypothesis that depression after stroke is associated with brain lesion location has been the focus of research and debates among scholars and clinical specialists for many years [1–8]. This hypothesis was widely publicized and attractive because it links neurobiology with clinical practice [1,2]. However, the evidence is conflicting. Many of the studies conducted by Robinson and his research team, scholastic viewpoints, and textbooks support the association between depression and left-hemisphere lesions [1,2,9–12]. In contrast, some studies suggest the opposite result, that depression is associated with right-hemisphere lesions [13–16]. Other studies do not confirm any association between depression after stroke and brain lesion location [17–20].

In view of the apparently conflicting evidence, questions about whether certain anatomic correlates can predict subsequent depression should be clarified. This information would help clinicians to identify, at an earlier stage, patients at highest risk for depression, and identify those stroke victims most likely to benefit from treatment interventions,

and perhaps contribute to better understanding of the etiology and biology of depression. If successful treatment can be instituted, rehabilitation may be shortened, costs reduced, quality of life improved, and unnecessary premature deaths prevented [16].

The two previous systematic reviews of this topic did not substantiate any definitive statement about the relationship between location of stroke lesion and risk of depression, but there were some drawbacks in the review techniques. One review was not a meta-analysis [5], while the other used meta-analysis but included only studies with a categorical diagnosis of depression [6].

Meta-analysis, a quantitative method of summarizing existing studies, is defined as an analysis of analyses. That is, the pooled results of individual studies that have previously appeared to be contradictory or confusing are re-analyzed to provide a systematic, quantitative review of the data, thus permitting strong, credible conclusions.

The purposes of this study were to employ meta-analytical techniques to update the previous meta-analysis results and to more completely address the relationship between post-stroke depression (PSD) and lesion location, and to further explore the heterogeneity that might exist among study results.

MATERIALS AND METHODS

Literature search

Several approaches were adopted to identify relevant studies. First, a search of the following databases, up to April 2003, was conducted: MEDLINE (from January 1966), PsycINFO (from January 1987), and EMBASE (from 1988). The key words used to identify articles included "stroke or cerebrovascular" and "depression or mood or affective". The search was restricted to studies published in English and involving human subjects. At this stage, abstracts of approximately 4,552 studies were identified and reviewed. Second, the relevant journals, such as *Stroke*, *Journal of Neurology*, *American Journal of Psychiatry*, and *Journal of Neurology, Neurosurgery and Psychiatry*, were hand searched for the period between May and July 2003. Third, all articles cited in the systematic review by Carson et al were surveyed and selected if they met our inclusion criteria [6]. Finally, the references cited in the articles identified by the above approaches were used to locate additional studies.

Up to this stage, approximately 233 potentially eligible studies were obtained.

Several inclusion criteria were adopted in this meta-analysis. First, the studies must have examined the association between depression after stroke and lesion location. Second, they must have provided information sufficient for the computation of effect sizes. Third, duplicate studies were excluded. These were defined as studies that shared a sampling frame, and had overlapping study dates, overlapping grant funding numbers, and similar or identical reported sample characteristics. Among duplicate studies, the study conducted with the largest number of participants was selected. If the studies were conducted on the same number of participants, the earliest one was chosen. Case studies, review articles, and pharmacological intervention studies were excluded. In total, 52 studies were included in our meta-analysis [1,10,13–62].

Characteristic variables coded from each study

A coding sheet was designed to record relevant data from each study: exclusion of patients with language dysfunction, assessor for diagnosing depression, instrument for diagnosing depression, time between stroke and diagnosis of depression, lesion location, source of patients, and study quality.

According to the methodological suggestions outlined by Singh et al [5], as well as our judgments based on a literature review of PSD, the criteria for evaluating the quality of a study in this meta-analysis included the following items: adequacy of study methodology (e.g. blind to neuroimaging assessment, valid depression diagnosis), clarity of description of subjects' characteristics (e.g. age, educational level), clarity of screening criteria for study subjects (e.g. excluding patients with previous psychiatric history, excluding patients with multiple strokes), and scope of the study (e.g. study that also assessed subjects' cognitive functions, social support functions). A total of 23 items, with score 1 or 0, was thus obtained to grade the quality of each study. Studies with scores of between 1 and 8 were considered low-quality studies, those with scores of 9 to 16 were medium-quality studies, and studies with scores of 17 to 23 were high-quality studies.

Inter-rater agreement

To ensure the reliability of the literature search process, during the first stage, approximately 10% of the 4,552 online abstracts found were randomly selected and independently read by two authors (YHW and SHY) to judge their eligibility for inclusion in the meta-analysis on the basis of the same criteria. The inter-rater agreement was 98%. In the final stage, the same reliability check was repeated for the 233 potentially eligible studies. The inter-rater agreement

was 96%. Furthermore, to ensure the reliability of the coding of the study characteristics, 26 studies were randomly drawn from the final set of 52 studies and independently coded by the same authors. Of seven study characteristics, inter-coder agreement was 92% for judging the exclusion of patients with language dysfunction, 85% for rating study quality, and 100% for the remaining study characteristics. Disagreements in coding were eventually resolved through discussion.

Computation and analysis of effect sizes

Each study result was represented in the form of effect sizes. The effect size calculated in this meta-analysis was referred to as *d*, indicating the difference of the means of depression scores between patients with left-hemisphere lesions and those with right-hemisphere lesions, and then divided by the pooled standard deviation, when depression scores were of continuous nature in a study. When a study reported only the frequencies or proportions of diagnosed depression, the difference in the proportion (or frequency transformed into proportion) between depressed patients with left-side lesions and those with right-side lesions was calculated instead. Effect size was positive if depression was more severe for patients with left-side lesions, and was negative if depression was more severe for patients with right-side lesions. The effect sizes from all studies were combined to obtain the overall effect size by averaging the *d* values, with each *d* weighted by the reciprocal of its variance [63]. The overall effect size, which was a weighted mean effect size denoting the degree of association between PSD and lesion location as a whole, was then tested for its statistical significance. A statistical test of homogeneity for all *d* values (indicated by Q_W) was performed to determine whether all the reviewed studies shared a common effect size [63].

To explore the heterogeneity among study results, we conducted analyses in which subgroups were formed according to each study characteristic. The weighted mean effect sizes, *d+*, in subgroups of each study characteristic were computed and tested for significance using 95% confidence intervals (95% CI). If the 95% CI of any subgroup did not include zero, the weighted mean effect size of that subgroup was statistically significant. Again, test of homogeneity of the effect sizes (Q_W) within each subgroup was performed. If Q_W was significant, it implied that studies within the same subgroup did not derive from a homogeneous population. Finally, the *d+* values were converted to the weighted mean correlations (*r+* values).

Some studies in our review yielded multiple outcome measures (i.e. multiple data points). These multiple outcome measures were obtained from different assessors, different assessment scales, different assessment time points, or different lesion locations within a hemisphere. As such, a single study may have yielded more than one effect size. Following common practice, we averaged effect sizes over multiple outcome measures within a study when computing the overall effect size. However, these multiple outcome measures were still applicable to the subsequent subgroup analyses. In total, 52 studies yielded 75 effect sizes. The total number of subjects included in this meta-analysis was 3,668 (1,775 subjects with left-side lesions and 1,893 subjects with right-side lesions). In this review, the computation of effect sizes was based on means and standard deviations for 48% of the studies, and proportions or frequencies for 48% of the studies; only 4.0% of effect sizes were obtained and converted from *F*, *t*, or *p* values. The DSTAT computer program [64], which was developed based on Hedges and Olkin's statistical techniques [63], was used for all data analyses.

RESULTS

Among all the effect sizes computed, the largest and smallest effect sizes were 1.54 and –0.98, respectively. Thirty studies yielded negative effect sizes and only 10 of these effect sizes reached the 0.05 level of significance; 22 studies yielded positive effect sizes and only four of these effect sizes reached significance. Across the 52 aggregated studies, the overall weighted mean effect size, –0.0801 ($p = 0.0145$, 95% CI = –0.146/–0.014), was significantly different from zero at the 0.05 significance level, indicating an association between PSD and right-hemisphere lesions, but this association was weak. Furthermore, the distribution of effect sizes was heterogeneous, $Q_{(51)} = 120.298$ ($p < 0.001$). After six outlier studies were excluded, homogeneity among effect sizes was obtained and yielded a weighted mean effect size, –0.0876 ($p = 0.011$, 95% CI = –0.16/–0.02), that was similar to the value obtained when all studies were included. The Table summarizes the results of subsequent subgroup analyses.

Most of the studies reviewed excluded patients with language dysfunction and adopted standardized rating scales for diagnosing depression (Table). Among the assessors for depression, there were more doctors, clinicians, and clients themselves than other assessors. Among the times for diagnosing depression after stroke, most studies assessed depression within the first 9 months after stroke. About half of studies were conducted with inpatient sub-

Table. Summary of statistics in each subgroup according to study characteristics

	k	$d+$	95% CI	$r+$	Q_W
Exclusion of patients with language dysfunction					
Yes	32	–0.1270	–0.2078/–0.0462	–0.0634	65.8073*
No	7	0.3414	0.0933/ 0.5896	0.1683	25.1621*
Assessors for diagnosing depression					
Doctor	19	–0.0523	–0.1656/ 0.0609	–0.0262	46.1167*
Clinician	13	–0.0575	–0.2056/ 0.0906	–0.0288	24.8055[†]
Nurse	4	–0.2130	–0.4145/–0.0114	–0.1059	2.8407
Client self-report	12	–0.1337	–0.2987/ 0.0313	–0.0667	38.2025*
Family members	3	–0.1219	–0.4029/ 0.1592	–0.0608	5.6035
Mixed assessors	4	–0.1737	–0.3187/–0.0286	–0.0865	2.0903
Instruments for diagnosing depression					
Clinical diagnostic criteria	15	–0.0440	–0.1609/ 0.0728	–0.0220	42.1669*
Structured interviews	1	0.2020	–0.6767/ 1.0808	0.1005	0.0000
Standardized scales	32	–0.1329	–0.2178/–0.0480	–0.0663	67.4285*
Observer rating scales	2	–0.1902	–0.6731/ 0.2927	–0.0947	1.6344
Research diagnostic criteria	2	0.3945	–0.1353/ 0.9243	0.1935	0.0151
Mixed measures	3	–0.2550	–0.4935/–0.0164	–0.1265	1.3821
Time (mo) of diagnosing depression after stroke					
≤ 1	13	0.1256	–0.0448/ 0.2960	0.0627	33.3436*
2–3	15	–0.1301	–0.2647/ 0.0046	–0.0649	38.7566*
4–9	16	–0.1272	–0.2235/–0.0309	–0.0635	25.4426
10–15	5	–0.0296	–0.2698/ 0.2107	–0.0148	0.6398
16–21	2	–0.3205	–0.6842/ 0.0431	–0.1582	0.4994
22–27	1	0.1967	–0.2393/ 0.6327	0.0979	0.0000
28–39	1	–0.0157	–0.5231/ 0.4918	–0.0078	0.0000
≥ 40	1	0.5055	–0.1096/ 1.1207	0.2451	0.0000
Sources of patients					
Inpatients	27	–0.0301	–0.1201/ 0.0599	–0.0151	86.0062*
Rehabilitation units	17	–0.1271	–0.2401/–0.0141	–0.0634	14.8532
Community	6	–0.1102	–0.3205/ 0.1000	–0.0550	10.3406
Lesion location of stroke[§]					
Left anterior vs right anterior lesions	7	0.0156	–0.1831/ 0.2143	0.0078	21.8388[‡]
Left intermediate vs right intermediate lesions	3	–0.1831	–0.4873/ 0.1211	–0.0911	0.4004
Left posterior vs right posterior lesions	6	–0.1805	–0.4340/ 0.0731	–0.0899	1.9775
All anterior vs all posterior lesions	6	–0.0056	–0.1795/ 0.1682	–0.0028	5.9095
Left anterior vs all other lesions	6	–0.0698	–0.2512/ 0.1115	–0.0349	9.7403
Left anterior vs left posterior lesions	6	0.0172	–0.2704/ 0.2361	–0.0086	12.7147
Right anterior vs right posterior lesions	6	–0.0244	–0.2729/ 0.2241	–0.0122	9.1650
Study quality					
High	4	0.0494	–0.2292/ 0.3281	0.0247	1.2958
Medium	45	–0.0802	–0.1498/–0.0106	–0.0401	111.7039*
Low	3	–0.2555	–0.5822/ 0.0712	–0.1267	1.6905

*$p < 0.001$; [†]$p < 0.05$; [‡]$p < 0.01$; [§]effect sizes for each study in the subgroups were derived from the comparison between the first item and the second item. k = number of studies/effect sizes in the subgroup; $d+$ = weighted mean effect size; 95% CI = 95% confidence interval; $r+$ = weighted mean correlation; Q_W = test of homogeneity of effect sizes.

jects. Most studies were judged to have medium quality, and a few studies investigated the relationship between depression and different locations of brain lesion in inter- or intra-hemispheric comparisons.

As shown in the Table, the weighted mean effect sizes within both subgroups for exclusion of patients with language dysfunction were significantly different from zero. This indicated that studies conducted with exclusion of language-impaired patients supported the relationship between PSD and right-hemisphere lesions, whereas studies conducted without exclusion of such patients showed the reverse trend, i.e. that depression was associated with left-hemisphere lesions. The follow-up comparison showed that the difference between both subgroups was significant. There was evidence of significant heterogeneity among the studies within each subgroup. This implied that studies within each subgroup of this study characteristic were not homogeneous. Studies using nurses as assessors and standardized scales as assessment instruments indicated a relationship between depression and right-hemisphere lesions (Table). This was also true of studies employing mixed assessors and mixed measures. However, no association was found between depression and lesion location when different brain regions were considered. Studies in which depression was assessed within the first 4 to 9 months of stroke showed that depression was associated with right-side lesions. Studies of medium quality also showed the same trend, as did studies of patients in rehabilitation units. Further, there was evidence of significant heterogeneity in the subgroups with more studies, indicating that the study results had more variability in these subgroups.

DISCUSSION

This study investigated the relationship between PSD and lesion location by conducting a meta-analysis of studies from the last 20 years [1]. While an earlier review by Carson et al did not support the claim that PSD was associated with lesion location [6], the results of our meta-analysis revealed that there was a significant, although weak, relationship between PSD and right-hemisphere lesions. Our finding might result from the factors of systematic sample exclusion as well as from the assessors and assessment tools for diagnosing depression. We found that many of the studies we reviewed employed standardized scales for assessing depressive disorders. This phenomenon, accompanied by systematic exclusion of patients with language dysfunction, might lead the overall effect size obtained in this meta-analysis to reach statistical significance, indicating that PSD was associated with right-hemisphere lesions.

Carson et al employed the methods of DerSimonian and

Laird to compute effect sizes indexed as relative risks [6]. In contrast, we used methods developed by Hedges and Olkin to compute effect sizes indexed as standardized mean differences, *d*. Our meta-analysis was conducted 4 years after Carson et al's study, and we aggregated studies that included both continuous and categorical data of depression. Carson et al analyzed 35 studies that included only categorical depression data. Although in their meta-analysis, the 95% CI for the overall estimate of the relative risk included 1 when all studies were included, the overall estimate of the relative risk, 0.93, seemed to indicate that more patients with right-side lesions were depressed.

As for language impairments, our finding supported those of earlier studies that reported a relationship between aphasia and depression [9,28]. In most of the studies we reviewed, patients with left-hemisphere damage had been excluded from samples because of the language comprehension or expression difficulties caused by stroke. It is conceivable that many of the excluded patients with left-hemisphere damage were also depressed. Consequently, the existence and severity of depression in patients with left-hemisphere damage may be underestimated, which in turn yielded the result that depression was associated with right-hemisphere lesions. In contrast, from studies that did not exclude patients with language dysfunction, we found a moderate association between PSD and left-hemisphere lesions. Most investigators of PSD have attempted to exclude patients with aphasia because patients with substantially impaired comprehension have difficulties completing most standardized interviews and scales [65]. Such a systematic, selective exclusion of patients with language dysfunction, which was commonly found in the studies we reviewed, would have introduced sampling bias into research designs of PSD studies and affected the reliability of PSD assessment [4].

As for the characteristics of the assessors and types of instruments, this study cross-analyzed the depression characteristics and language characteristics and found that a majority of studies adopting standardized depression scales excluded patients with language impairments. This sampling method may be the reason for the statistically significant relationship between depression after stroke and right-side lesions found in the studies using standardized depression scales, nurse assessors, and mixed assessors. As for the categories of doctors and clinicians, the finding showed no correlation, which could be influenced by different evaluation dimensions and breadth, such as clinical interviews, observations, and judgments. In this review, we found that there was a significant relationship between types of assessment instruments and assessors.

Most doctors used clinical diagnostic criteria (e.g. the Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases systems), while most of the clinicians, nurses, and patients used standardized scales (e.g. Hamilton Rating Scale for Depression, Beck Depression Inventory, Zung Self-Rating Depression Scale, Center for Epidemiologic Studies Depression Scale, Minnesota Multiphasic Personality Inventory). The issues concerning the potential effect of using different assessment tools and different assessors in the evaluation of PSD were not investigated by Carson et al [6].

In Carson et al's study, no evidence supported the hypothesis that the time between stroke and diagnosis of depression was an important confounder. Lesion location was not associated with depression no matter when the depressive symptoms after stroke were assessed. However, our meta-analysis showed that depression was statistically associated with right-hemisphere lesions when depression was assessed within 4 to 9 months after stroke. When depression was assessed within the first month after stroke, the weighted mean effect size was positive, which implied that depression was associated with left-side lesions, but the association was not statistically significant. This finding contradicts the general findings obtained by Robinson and associates [1,2].

In the meta-analysis conducted by Carson et al, there was evidence showing a risk of depression with right-side lesions among patients selected from the community, but not among patients in hospital or in rehabilitation units. However, our meta-analysis showed that depression was associated with right-side lesions among patients in rehabilitation units but not among patients in hospital or in the community.

Consistent with Carson et al, our meta-analysis found no relationship between PSD and lesions in any locations of the hemispheres (anterior, intermediate, and posterior). In other words, in both Carson et al's and our meta-analyses, the severity of depression did not differ in terms of different brain regions assessed. However, in both Carson et al's and our meta-analyses, the sample size only included seven studies or less.

As for the evaluation of study quality, we found that most studies were of medium quality, and that there was an association between PSD and lesion location in these studies. Similar to the findings of Carson et al, we found no relationship between PSD and lesion location among high-quality studies.

Generally speaking, although this study supported the relationship between PSD and right-side lesions, the relationship was weak and may not have much practical significance. Also, it should be kept in mind that whenever the sample size in a subgroup is small, the result of that subgroup should be interpreted with caution.

In summary, our findings showed that PSD was slightly associated with right-side lesions, while Carson et al showed no association. These findings contradict the common beliefs generally held by doctors and clinicians in medical settings. Further research is needed to validate these findings.

While reviewing the literature, we found that, while brain lesion location and stroke severity can be diagnosed by instruments, depression assessment cannot be complete without the use of language. Through language, the patient's inner feelings and thought processes can be understood and further utilized as a criterion for diagnosing depression severity and type. Taking into consideration that different stroke damage features directly or indirectly influence the accuracy of depression diagnosis, some studies excluded patients with severe aphasia or with comprehension difficulty. In contrast, studies that did not take this into consideration did not exclude patients with aphasia. Most studies adopted traditional criteria or assessment instruments for diagnosing depression after stroke. These traditional diagnostic criteria or instruments were originally developed for use in non-brain-damaged patients and have not been adapted to take into account the ways in which the symptoms of brain damage may affect and alter the clinical presentation of depression [4]. Patients with brain injury could change, or even lose, some of their functions (e.g. language, cognition, emotion, awareness, social function). Due to the possible changes in self-awareness, language expression, interpersonal interaction, emotion, personality, or physical functioning, assessment results become biased or cannot be applied. On the basis of our study results, we suggest that multiple information sources, accurate neuroimaging techniques, or multidimensional neuropsychologic assessment instruments be adopted to reduce the influence of the change in some functions on assessment accuracy. If methods designed to evaluate the depression of non-brain-injured patients are to be used to reliably assess those with brain damage, these methods should be specifically validated for neurologically impaired populations [3,4].

Although the reviewed studies claimed that their topics were the same or similar (investigation of the relationship between depression after stroke and brain lesion location), their operational definitions were different, such as criteria for sampling, definitions of disease, ways of assessment, types of assessment instruments, and assessment time.

These discrepancies may lead to differences in the nature and characteristics of studies. When the statistical test of homogeneity is significant, the sources of heterogeneity among study results should be investigated [66]. The exploration of heterogeneity presents opportunities to increase the relevance of the conclusions drawn and enhance the understanding of the studies reviewed [67].

At the beginning of our meta-analysis, many possible influential study characteristics were analyzed, such as type of stroke, blinding of neuroimaging assessments, lesion volume, proximity of the lesion to the frontal pole, past psychiatric history, family psychiatric history, and history of stroke. However, because quite a few of the reviewed studies did not provide clear or detailed descriptions of research methods and procedures, the analyses became difficult. Also, because some of these study characteristics were examined in only a few studies and were further subdivided, the sample size of each subgroup became very small, and the generalizability of the findings became limited. Due to these limitations, the above study characteristics were not further analyzed. There has been a consensus among meta-analysts that enhancing the standards for primary study reporting is necessary to provide sufficient information for subsequent replication and reanalyses.

For future primary studies and meta-analyses, in addition to the discreet investigation on the relationship between PSD and brain lesion location, underlying mechanisms interacting between lesion location and PSD, as well as their influences, and how to effectively help patients to become healthy should be investigated.

ACKNOWLEDGMENTS

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中風後憂鬱與大腦損傷位置相關性之整合分析研究

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大腦損傷的解剖學定位與中風後憂鬱的發生之間的關聯性仍是未解決的問題，對於這個爭議的現象值得作進一步探索與釐清；因此，本研究的目的是從中風後憂鬱與大腦損傷位置的關聯性之研究領域中，根據現有的研究結果，做一系統性的量化回顧，並探究造成研究結果之差異性來源，以尋求一致性且更強而有力的結論。研究中所回顧的文獻範圍係取自 MEDLINE 、 PsycINFO 、 EMBASE 資料庫，系統性地蒐集相關文獻，且檢視重要文獻中參考資料所列之文獻，從每篇研究報告中登錄重要特徵變項，計算中風後憂鬱與大腦損傷位置的關連效果量，採整合分析技術進行分析。本整合分析中包含 52 篇研究文獻，參與研究之患者達 3,668 位，研究結果顯示中風後憂鬱與右腦損傷有輕度的關連性存在，而造成研究結果之異質性來源主要包括語言功能障礙患者的排除控制、使用不同之憂鬱評量工具與方式等因素。未來的研究應著重於訂定明確的研究報告規範，進一步地改善對於失語症患者的憂鬱評量工具和採用合宜的方法學，以清楚地探究中風後憂鬱與損傷位置之關連性。

關鍵詞：中風後憂鬱，損傷位置，整合分析
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