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What is This?

An Enriched Environment Improves Sensorimotor Function Post–Ischemic Stroke

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Abstract

Objective. An enriched environment (EE) refers to conditions that facilitate or enhance sensory, cognitive, motor, and social stimulation relative to standard (laboratory) conditions. Despite numerous published studies investigating this concept in animal stroke models, there is still debate around its efficacy. The authors performed a systematic review and meta-analysis to determine the efficacy of an EE on neurobehavioral scores, learning, infarct size, and mortality in animal models of ischemic stroke. *Methods*. Systematic review of controlled studies of the use of an EE in experimental stroke was conducted. Data extracted were analyzed using weighted mean difference meta-analysis. For pooled tests of neurobehavioral scores, a random effects standardized method was used. *Results*. Animals recovering in an EE poststroke had mean neurobehavioral scores 0.9 standard deviations (95% confidence interval [CI] = 0.5-1.3; *P* < .001) above the mean scores of animals recovering in standard conditions and showed a trend toward improvement in learning (25.1% improvement; 95% CI = 3.7-46.6; *P* = .02). There was no significant increase in death. Animals exposed to an EE had 8.0% larger infarcts than control animals (95% CI = 1.8-14.1; *P* = .015). *Conclusions*. The results indicate significant improvements in sensorimotor function with EE poststroke but suggest a small increase in infarct volume. Clarification of the underlying mechanisms requires further study but should not overshadow the observed functional improvements and their application to clinical trials during stroke rehabilitation.

Keywords

animal model of stroke, enriched environment, functional recovery

Introduction

In 1947, neuropsychologist Donald Hebb compared rats housed in standard laboratory conditions to those he set free to roam and live in his house and found that the latter had better learning and problem-solving skills.[1] These results prompted further research into the concept of an enriched environment (EE). An EE refers to conditions that facilitate or enhance sensory, cognitive, and social stimulation relative to standard (laboratory) conditions.[2]

Even though there are no standardized protocols, an EE most often involves social housing (8 to 12 animals) in large cages that are filled with inanimate objects, for the purpose of increasing sensory, physical, and social stimulation. Such objects include but are not limited to ladders, ropes, tubes, balls, horizontal boards, swing boards, chains, toys, and on occasions, running wheels. Participation in activities within the EE is voluntary. Training of skilled motor tasks or other sensorimotor therapies is not included within this environment. Environmental novelty and cognitive stimulation is maintained through the rearrangement and changing of cage contents at varied intervals, depending on the laboratory.[2]

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EE has shown benefit for brain development and recovery from injury in a number of animal models.[3] Unlike other rehabilitation techniques investigated in animals such as constraint and specific limb training, use of an EE differs, in that it facilitates voluntary and challenge-free activity in stimulating surrounds.[4] Application of this concept in animal stroke models has yielded inconsistent results. The majority of published studies report efficacy for enhancement of function and learning; however, some have had neutral or negative results.[5,6] Most have used relatively small numbers of animals, and estimates of effectiveness have varied.

The method of meta-analysis is well established in clinical trials. It enables increased precision in the determination of effectiveness of therapy by pooling data from a number of studies in an unbiased manner. Recently, this method has also been applied to animal studies and has made a significant contribution to the evaluation of effectiveness of therapies and to understanding how aspects of experimental design may affect study outcome.[7-9]

Our aim was to conduct a systematic review and meta-analysis to establish the quality of studies examining the use of an EE in animal stroke models and determine the effect an EE has on neurobehavioral scores, learning, infarct size, and mortality in these models. Determining the quality and efficacy of this environmental intervention is a necessary step before any attempts are made to translate this concept into the clinical setting.

Methods

This meta-analysis was based on previously published methods.[8] Searches were performed on October 2, 2008, from the electronic databases PubMed, MEDLINE, BIOSIS, and EMBASE using the following search strategy: (recovery of function OR behavior OR treatment outcome OR motor activity) AND (stroke OR cerebral infarct OR cerebrovascular accident OR CVA OR brain ischemia OR focal cortical ischemia OR cortical infarct OR cerebral ischemia OR MCA occlusion OR middle cerebral artery occlusion OR brain hypoxia) AND (animal OR mice OR rat OR animal model) AND (enrich* AND environment*). Manual search of the cited references from retrieved publications was also performed to identify any additional studies.

Inclusion Criteria and Outcome Measures

All controlled studies of therapeutic EE in animal models of focal cerebral ischemia that presented data for any of our nominated outcomes were considered for inclusion. Intracerebral hemorrhage models were excluded, as were models of global ischemia (primarily a model of cardiac arrest). Neurobehavioral score (for performance on a neurobehavioral test examining sensorimotor function) was the primary

outcome. Secondary outcomes were learning, infarct size (volume or area), and death. Animals housed in standard laboratory conditions were designated as the control group.

Data Extraction

For each comparison, and for each control and treatment group, investigators (HJ and NJS) identified and extracted the number of animals per group, mean outcome, and standard error (SE) or standard deviation (SD). Where an outcome measure was measured serially, only the last measure was used because methodological limitations prevented pooling of data, and the last measure was considered most representative of the clinically relevant outcome of long-term functional recovery. When data were only presented graphically, attempts were made to obtain data from authors; if these were not available, values were measured from the published graphs. When animals were exposed to a physical or cognitive intervention in addition to exposure to an EE (cotreatment), this was noted. Cohorts receiving cotreatments with pharmacological or cell-based therapies were not included; however, where such studies presented data on both EE and standard-housed controls, data from these cohorts were included. Multiple publications (repeat publications) from the same study were noted, and all relevant data were allocated to the original group of animals studied. When a single control group served multiple treatment groups, the size of the control group entered into the meta-analysis was adjusted by dividing by the number of treatment groups served. Only animals that had died after allocation to the various housing conditions were used in the estimates for mortality, and animals that died during surgery or in the immediate postsurgical period were excluded from all calculations.

Housing density was a factor considered important in control conditions; hence, distinctions were made a priori between standard small-group housing (2-4 rats per cage) and social housing (n ≥ 5). Prospective and retrospective exclusion of animals was noted. For example, use of a neurobehavioral score as an inclusion criterion before assignment to an EE was classed as prospective, whereas exclusion on the basis of small histological lesion (postintervention) was classed as retrospective exclusion. Studies that excluded animals retrospectively were not included in the meta-analysis for infarct size because of the possibility of confounding. To minimize the loss of statistical power that results from the analysis of multiple outcomes, a single measure of the Morris Water Maze test was chosen for the outcome of learning. The distance swum (path length) to reach the target (in meters) was used. The authors considered the 3 parameters commonly reported: path length, latency, and speed. Path length would be the least affected by residual motor impairments and hence would be more representative of the animal's cognitive abilities.

Quality was assessed against the Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Stroke (CAMARADES) study quality checklist,[10] which comprises (1) publication in a peer-reviewed journal, (2) statement of control of temperature, (3) randomization to treatment group, (4) blinded induction of ischemia, (5) blinded assessment of outcome, (6) avoidance of anesthetics with marked intrinsic neuroprotective properties, (7) use of animals with hypertension or diabetes, (8) sample size calculation, (9) statement of compliance with regulatory requirements, and (10) statement regarding possible conflicts of interest. Statements of randomization to treatment group were taken at face value. Absence of such a statement was interpreted as an indication that randomization did not occur.

Other pertinent data, including species, time of commencement of the EE relative to stroke, time of assessment, housing conditions of control animals, type of ischemia, duration of ischemia (for temporary occlusions), method of ventilation, method of anesthetic induction, dose (hours/day) and length (days) of the EE, and inclusion of a running wheel (yes/no), were also extracted for the purpose of exploring the effect such variables had on each outcome via stratified analyses.

Statistical Analysis

All meta-analyses were performed using a random effects model. For the primary outcome, neurobehavioral scores, data were pooled using a standardized mean difference (SMD) meta-analysis. In the case of the use of multiple tests of sensorimotor function, only 1 pooled outcome measure was entered into the analysis for each experimental animal. Weighted mean difference (WMD) was considered inappropriate for this pooled analysis, given the differences in neurobehavioral tests' measurement scales. Where specific neurobehavioral tests were performed in at least 3 individual publications, results were pooled. These data and that for infarct volume and learning were analyzed using WMD. Odds ratios and confidence intervals (CIs) were estimated for mortality. Significance level was set at $P < .05$ for the primary outcome (neurobehavioral score) and the associated exploratory analyses. For ease of comparison, data are presented with 95% CIs. To account for multiple secondary comparisons, significance level was set at $P < .017$ for the outcomes of learning, infarct size, and death. Stratified analyses to determine potential sources of heterogeneity were performed on aspects of study quality and design for the pooled and the individual neurobehavioral score data sets, infarct size, and learning. The significance of differences between n groups was assessed by portioning heterogeneity and by using the χ^2 distribution with $(n - 1)$ degrees of freedom, with the significance level set at $P < .01$. Overall heterogeneity was examined using the I^2 statistic.[11]

Results

In all, 21 studies both met the inclusion criteria and presented complete data sets (Figure 1 and Table 1). The median quality score was 5 of a possible total of 10 (interquartile range 5-6), with all but 1 study (with a score of 8)[12] scoring between 4 and 6 of a possible 10. Nine (43%) of the included publications reported randomization and 7 (33%) reported blinded assessment of outcome. Nearly all studies that reported randomization failed to specify details of this process. No study reported sample size calculations or whether surgeons were blinded to group allocation. The small number of experiments that contributed to each outcome resulted in insufficient power to statistically assess publication bias.

Efficacy

Neurobehavioral scores. We found that 13 studies (contributing 17 individual experiments) had complete data sets for the outcome of neurobehavioral scores. Exposure to an EE poststroke significantly improved function, with mean neurobehavioral scores that were 0.9 SDs greater than those of control animals (95% CI = 0.5-1.3; $P < .001$; Figure 2A). The most frequently used tests were rotating pole (7 experiments), limb placement (5 experiments), horizontal beam (4 experiments), and ladder test (4 experiments). An EE significantly improved neurobehavioral scores in the rotating pole, horizontal beam, and limb placement tests (Figure 2B). The ladder test point estimate of effect was in the direction of benefit but was not statistically significant ($P = .408$).

Stratification of the pooled neurobehavioral data revealed that 2 outlying studies[6,23] were the major contributors to heterogeneity (Figure 2A). Removal of associated data improved homogeneity ($I^2 = 65\%$ to $I^2 = 0$).

Exploratory analyses of the rotating pole test did not reveal any significant contributors to heterogeneity. Both time to administration ($P = .008$) and length of exposure ($P = .008$) to EE were significant sources of heterogeneity in the ladder test. The stratification according to these 2 variables separated out identical studies, so the major contributor to the observed heterogeneity could not be identified.

Learning. Only one[14] of the 8 studies used the labyrinth and radial arm test to assess learning. All others used the Morris Water Maze. Therefore, to improve homogeneity and enable use of WMD analysis, labyrinth and radial arm test results were excluded from further analysis.

Animals housed in an EE poststroke had a 25.1% improvement in learning relative to controls (95% CI = 3.7-46.6; $P = .022$; Figure 3), although this estimate showed moderate heterogeneity. Exploratory analyses revealed a 51.1% (95% CI = 30.9-71.4) improvement in randomized animals (3 experiments), compared with only 8.6% (95% CI = −13.1 to 30.3) in those that were not randomized (5 experiments; $P = .004$).
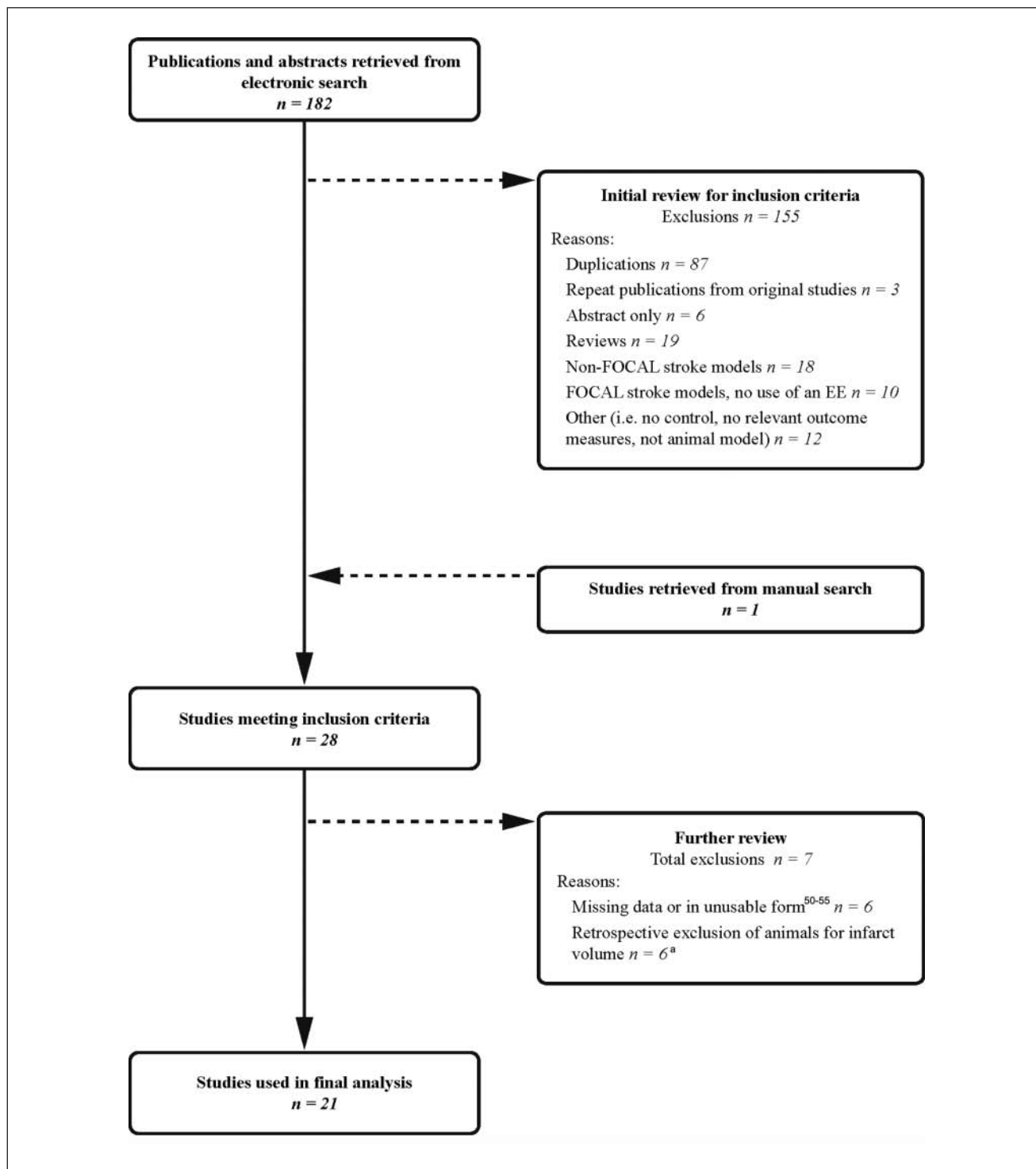
Figure 1. Schematic of study selection
[a]Only 1 of 6 was completely excluded from the analysis as the remaining 5 presented data for other outcome measures

Infarct size and mortality. Animals recovering in an EE had an 8.0% larger infarct postintervention than control animals (95% CI = 1.6-14.5; P = .015; Figure 4). There was low heterogeneity for this outcome ($I^2 = 0$), and exploratory analyses did not reveal anything of significance. A total of 7 studies (15 experiments) presented appropriate data for statistical

Table 1. Number of Individual Experiments Per Publication Contributing to Each Outcome Analysis

| | | | | Neurobehavioral Score | | | | | | |
| | | | | Individual Test Analyses | | | | | | |
Study	Year	Quality Score	Pooled Analysis	Rotating Pole	Limb Placement	Traverse Horizontal Beam	Ladder (Horizontal)	Infarct Volume	Learning	Mortality
Biernaskie et al[13]	2004	5	3				2			
Buchhold et al[14]	2007	5	2	1						
Dahlqvist et al[15]	1999	5						6		
Dahlqvist et al[16]	2004	6	1					2	1	
Hicks et al[6]	2008	5	1					3		
Johansson[17]	1996	4	1	1	1			1		
Johansson and Ohlsson[18]	1996	6	1	1	1	1				1
Komitova et al[19]	2005	5								1
Matsumori et al[20]	2006	4						1		
Nygren and Wieloch[21]	2005	5								7
Nygren et al[22]	2006	5	1	1						1
Ohlsson and Johansson[23]	1995	6	2	2	2	2		1		2
Puurunen et al[24]	2001	5	1		1	1			1	
Puurunen et al[5]	2001	5	1					1	1	
Risedal et al[25]	1999	4							2	2
Risedal et al[26]	2002	6								1
Ronnback et al[27]	2005	6							1	
Sonninen et al[28]	2006	4							1	
Wang et al[29]	2008	7	1					1		
Windle et al[30]	2007	5	1				1			
Wurm et al[31]	2007	5	1				1	2	1	

analysis. Recovering in an EE poststroke did not have any significant effect on mortality (OR = 1.0; 95% CI = 0.5-1.9; $I^2 = 7\%$).

Exploratory Analyses

Experimental design between studies varied significantly (see Table 2). The a priori distinctions made regarding housing conditions of control animals became redundant as only 1 of the included studies used social conditions (n = 10 animals). The majority used standard housing, and 6 housed animals individually. Only one included an experimental paradigm in which animals received enriched housing both prior to and following stroke,[23] and just more than half of the included studies incorporated a running wheel into the EEs. Other parameters that varied included the time of commencement of environmental enrichment, ranging from 1 to 30 days; length of exposure to enrichment from 1 to 90 days; and changes in cage contents and frequency of exchange or rearrangement of contents from once a week to daily. Exploratory analyses to determine the contribution of these aspects and the effect of previously listed pertinent variables (see Data Extraction section) were performed, but insufficient data and many sources of variability prevented any meaningful conclusions.

Discussion

Our aim was to determine the efficacy of an EE poststroke using systematic review and meta-analysis. We are the first to attempt to analyze systematically all EE-based studies in animal models of ischemic stroke. The results demonstrate the significant beneficial effects of EE on neurobehavioral scores, overall, and on 3 of the 4 most frequently used individual tests. There was a strong trend for improvement in learning and a small but statistically significant increase in infarct size. There was no increased likelihood of death.

Moderate levels of heterogeneity were present in results for pooled neurobehavioral scores, the rotating pole and ladder tests, and learning. This was anticipated given the variability of study designs and small numbers of comparisons. Pooling of data revealed favorable effects on sensorimotor

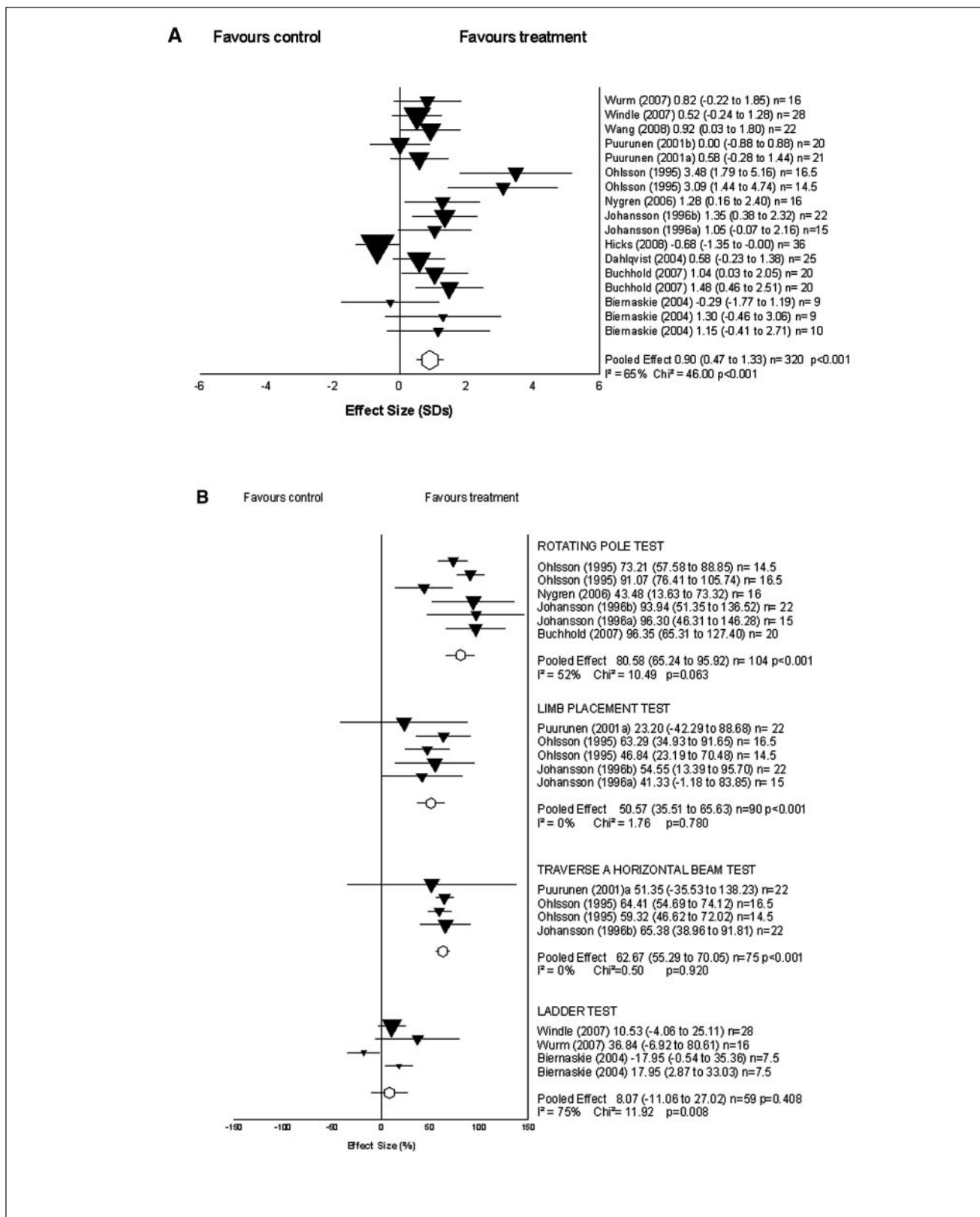**Figure 2.** A. Estimates and 95% confidence intervals of effect size for an enriched environment (EE) on pooled neurobehavioral score.
B. Estimates and 95% confidence intervals of effect size for an EE on neurobehavioral score by individual test
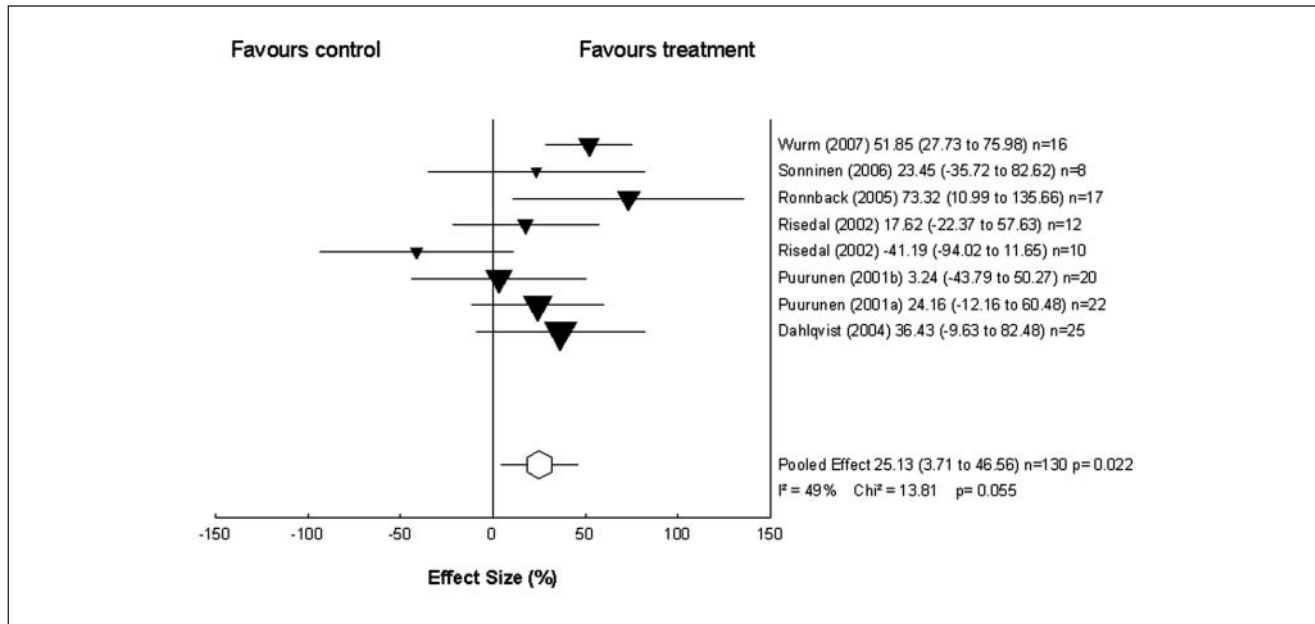
Figure 3. Estimates and 95% confidence intervals of effect size for an enriched environment (EE) on learning
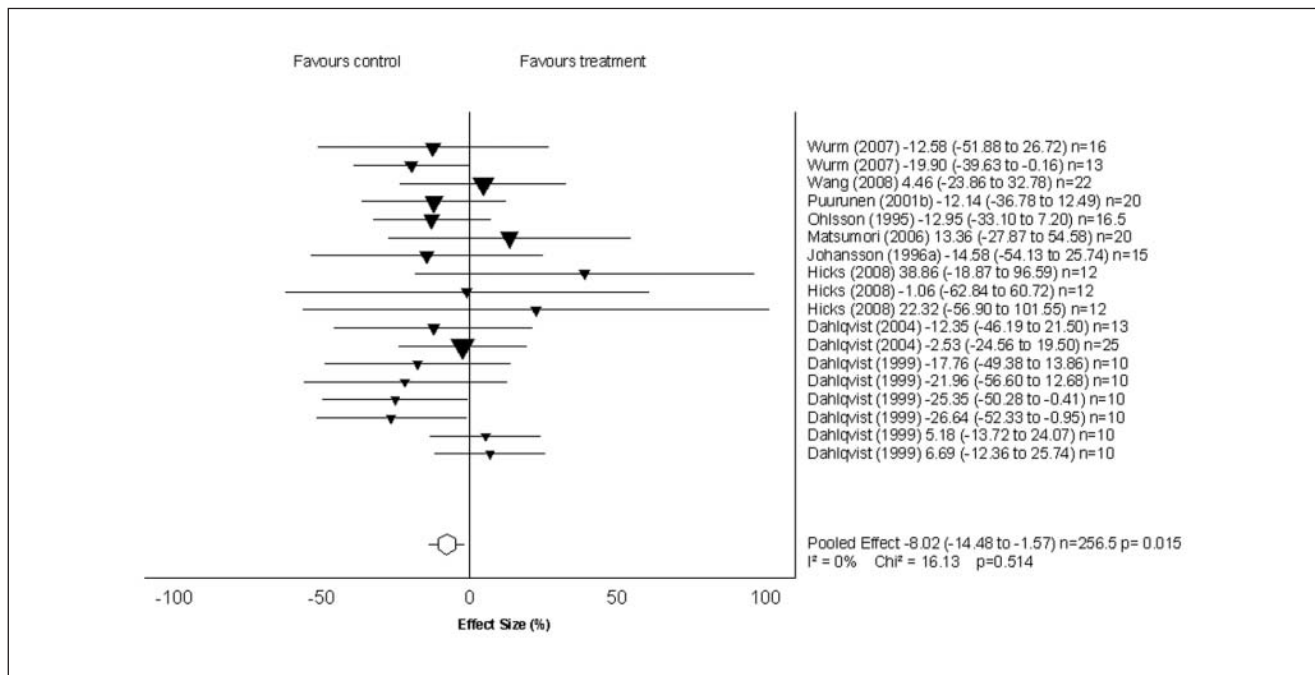
Figure 4. Estimates and 95% confidence intervals of effect size for an enriched environment (EE) on infarct size

function of animals recovering in an EE, even despite the largest experiment (n = 36) showing a trend favoring control. Small numbers and study heterogeneity prevented meaningful analysis of the contribution of individual components of the EE, such as exercise (running wheel), to outcome. Data from studies of intracerebral hemorrhage and global ischemia were not included in the meta-analysis in order to limit heterogeneity, and anticipated numbers of studies in these models were far too small to conduct separate analyses. Nevertheless, published studies on the effect of an EE on functional outcomes in such models are generally consistent with those found in focal ischemic models.[32-36]

Table 2. Summary of Variation in Study Design

Study	Year	Control Conditions	EE Commenced (days post stroke)	Hours Per Day	Length of EE (days)	Size of Cage (mm)	N/ cage	Changes (Per week)	EE Contents
Biernaskie et al[13a]	2004	ST	5 and 30	24	35 and 10	NS	4-6	2	Ropes, beams, platforms, and various toys
Buchhold et al[14]	2007	D	1	24	27	NS (large)	8	NS	Catwalk, playing toys, hiding tunnel, and running wheel
Dahlqvist et al[15]	1999	ST	1	24	1, 2, 6, 11, 19, and 29	815 × 610 × 450	NS	NS	Chain, swing, horizontal boards, inclined boards, wooden blocks
Dahlqvist et al[16]	2004	D	2	24	29 and 34	820 × 610 × 450	12	7	Wooden tunnels, ladders, chain, swing, elevated horizontal boards, inclined boards, running wheel
Hicks et al[6]	2008	ST	8	24	27, 55, 83	NS (large)	8	1	Tubes, beams, shelves, ropes and ladders, and access to running wheel one 6-hour session per week
Johansson[17]	1996	ST	15	24	20	815 × 610 × 450	7	1	Chain, swing, horizontal boards, connecting boards, wooden blocks, swing boards
Johansson and Ohlsson[18]	1996	SL	1	24	90	815 × 610 × 450	9	1	Chain, swing, horizontal boards, connecting boards, wooden blocks and metal objects, swing board
Komitova et al[19]	2005	ST	1	24	7	815 × 610 × 1280	10	2	Chains, swing, horizontal and vertical boards, wooden blocks, and objects of different sizes and materials
Matsumori et al[20]	2006	ST	7	24	56[a]	2-story, 760 × 560 × 770	10	1	3-Dimensional labyrinth maze, ladder, chains, hammock, running wheel, wooden blocks, and nylon bones
Nygren and Wieloch[21]	2005	ST	2	3 and 24	12-54	Multilevel cage, 880 × 650 × 1400	10-15	3	Plastic tubes, ladders, chains, robes, platforms, running wheel, toys
Nygren et al[22]	2006	ST	2	3	26	Multilevel cage, 880 × 650 × 1400	10-15	3	Plastic tubes, ladders, chains, ropes, platforms, ramps, running wheel, toys
Ohlsson and Johansson[23]	1995	D	1	24	83	815 × 610 × 450	12	1	Chain, swing, horizontal boards, connecting boards, wooden blocks, swing boards
Puurunen et al[24]	2001	ST	1	24	25	2 cages, 610 × 460 × 460, connected by tunnel	6	3	Shelves, running wheel, manipulative objects (glass balls, jars, wooden objects), one wall constructed of bars
Puurunen et al[5]	2001	ST	1	24	32	2 cages, 610 × 460 × 460, connected by tunnel	6	3	Shelves, running wheel, manipulative objects (glass balls, jars, wooden objects), one wall constructed of bars
Risedal et al[25a]	1999	ST	1 and 7	24	41 and 35	820 × 610 × 450	8	2	Chain, swing board, horizontal boards, inclined boards, wooden blocks
Risedal et al[26]	2002	D	2	24	26	820 × 610 × 450	8	2	Horizontal and vertical boards, chain, swing, and swing board
Ronnback et al[27]	2005	D	2	24	31	820 × 610 × 450	8-10	7	Wooden tunnels, ladders, chain, swing, elevated incline, running wheel
Sonninen et al[28]	2006	D	2	24	23	2 cages, 610 × 460 × 460, connected by tunnel	4	3	Ladders, shelves, running wheel, manipulative objects (glass balls, jars, wooden objects)
Wang et al[29]	2008	ST	7	24	28	2 story, 760 × 560 × 770	5-6	1	3-Dimensional labyrinth, ladder, running wheel, a house, chains, hammock, nylon bones, wooden blocks
Windle et al[30a]	2007	ST	8	24	63	NS (large)	6-8	2	Ropes, beams, platforms, and various toys
Wurm et al[31]	2007	ST	1	24	9 and 41	850 × 750 × 400	6-8	7	Tunnels, ladders, chains, seesaw, places of escape

Abbreviations: EE, enriched environment; NS, not specified; ST, standard; SL, social; D, deprived.
[a]Cotreatment used.

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The finding that EE-exposed animals showed better learning in those studies in which treatment allocation was properly randomized was unexpected. Most previous studies have shown an inverse relationship between randomization and overall effect size,[8,37] consistent with the principle that the lower the quality of the study, the greater the apparent benefit of the intervention. However, this finding was from a single exploratory analysis, and the result should be interpreted cautiously.

Although there has been a previous report of increased infarct size associated with early training and EE,[25] this is the first study to show a small increase in infarct size with EE, even in the absence of early training. There were 4 studies included in the meta-analysis, which included an additional training component, but data from only one of these were suitable for inclusion in the estimate of infarct volume. This study did not commence training until the second week postsurgery and indeed showed a trend toward smaller infarcts in treatment animals[20] (see Figure 4). The overall effect of EE on infarct volume was small (8% increase) but statistically significant. Lending robustness to the finding, 12 of 18 studies reported increased infarct volume of some degree, although none of the individual studies reported a statistically significant effect. The result suggests the possibility of increased late tissue loss (because EE did not commence until at least 24 hours after stroke induction), possibly contributed to by the stress of a new environment and social housing. Interestingly, the 3 experiments (presented in a single publication from the 1 laboratory) using the endothelin model, in which cell death has been reported to mature more slowly, did not show an increase in infarct volume.[32] Other possibilities, such as a change in the rate of tissue repair, must also be considered as possible explanations for the apparent increase in infarct volume.

Unfortunately, great variability in experimental design across studies limited our ability to investigate any relationship between sensorimotor function or learning and infarct size. Results from observational and training animal models of stroke that have not included EEs indicate that larger lesions (measured during the chronic phase) are associated with more significant chronic neurological deficits, irrespective of method of stroke induction.[38-40] Although there are numerous studies indicating a moderate correlation between infarct size and functional outcome clinically,[41-44] a recent review argues that such findings may be confounded by weak methodological design and a disregard for importance of location.[45] Hence, given this evidence, the finding that exposure to an EE results in a small but significant increase in infarct volume raises the question of whether this finding is functionally significant and whether the apparent infarct expansion includes loss of any viable brain tissue. Regarding mortality, the point estimate for effect was 1.00, implying no effect; however, the wide CIs suggest some caution in interpretation.

Not all human poststroke functional outcomes can be assessed in animals (ie, speech, mood, and quality of life). However, these models are still of great value because the neurobehavioral tests used in the majority of studies include elements that address aspects of sensorimotor function and learning that are highly relevant to humans recovering from stroke (including coordination, proprioception, gait, skilled reach and accuracy, and spatial memory).

Most studies achieved a moderate quality score. These results are consistent with previous meta-analyses of studies using animal stroke models, with many published papers of low to moderate reported quality.[8,37,46] The small numbers of studies that reported randomization, blinded assessment of outcome, or a priori sample size calculations are concerning; however, for the first two, the results are substantially higher than those from studies of other disease models.[47] Nevertheless, these data suggest that several important aspects of experimental design are not yet routine in experimental studies. The CAMARADES quality scale was used in this analysis, not because it reflects commonly used factors in clinical trial design but because it reflects the likelihood of the experimental results being unbiased. It is hoped that the recent publication of good laboratory practice[48] will address many of the quality issues raised from this study and encourage inclusion of all pertinent information in future publications.

General limitations to the technique of meta-analysis have been previously reviewed.[7,37] Attempts were made in this meta-analysis to address a number of these issues by accounting for factors such as prospective and retrospective exclusion, the use of cotreatments, and consideration of the impact that interstudy and intrastudy heterogeneity had on both analysis design and interpretation. Additionally, considering that the experimental setup of an EE in animal models is by nature very complex, meaningful statistical analysis of the multitude of variations observed in the included studies was not possible. Finally, aspects such as negative publication bias and bias introduced from aspects of trial design were potential sources of falsely elevated benefits of intervention. Unfortunately, there were insufficient experiments to permit a formal assessment of the effect of publication bias using the Egger method.[49]

Overall, 6 publications[50-55] were excluded because data for the experimental outcomes were either missing or were presented in a form inappropriate for statistical analysis (ie, medians or means without a SE or SD). Where necessary, investigators were contacted in an effort to maximize animal numbers and clarify experimental methodology; however, for the 6 above-mentioned studies, we were unable to obtain usable data. A limitation to the WMD meta-analysis method prevented the inclusion of data from 1 experiment for the rotating pole analysis.[14] These data were included in the SMD meta-analysis used to estimate the pooled effect size for neurobehavioral scores.

The results from this study now give statistical support to the consensus that an EE aids in the recovery of motor functioning.[2,3] However, this reopens the debate about whether control conditions in animal models are more representative of environmental deprivation than a "normal" environment. Standard housing conditions have improved significantly over the last 30 years (the main change being an increase in cage size to allow animals to stand on their hind legs), so the argument that EEs really highlight the negative consequences of environmental deprivation may be less relevant than in the past. Complicating this further is the difficulty in determining what constitutes a normal or natural environment for animals that have been bred specifically for, and therefore are possibly behaviorally adapted to, laboratory conditions.[56] Clearly, the degree of stimulation is much less than in rats living in a natural environment. This could also be argued for current medical and rehabilitation wards, as evidence continues to emerge that suggests that patients in these settings are relatively "environmentally deprived" compared with "free-living" healthy people.[57]

The results of this meta-analysis provide strong evidence for the effectiveness of exposure to an EE in improving neurobehavioral score after experimental stroke. Future methodologically rigorous studies will be required to address the relative contribution of different components of the EE.

Implications

Results from this systematic review and meta-analysis give strong support to the conclusions drawn by multiple small studies conducted over the past 15 years, which have shown that exposure to an EE following focal stroke enhances sensorimotor function. Given that the outcome of most interest clinically is poststroke function, the results of this meta-analysis are encouraging. The observed small increase in infarct volume has many potential explanations that may be unique to the experimental setup. This requires further investigation, but we do not believe that this should overshadow the observed functional benefits. Additionally, these conclusions may prompt clinicians to consider how physically, socially, and cognitively stimulating the environments of current human stroke survivors are—past studies suggest that many rehabilitation settings may in fact be relatively environmentally deprived compared with a normal human environment.[57,58] Enrichment of these environments may require review of current policies, rearrangement of ward setups, rethinking of ward routines, and the provision of additional equipment. It seems unlikely that enrichment of the ward environment could do harm, and many may argue that an EE should be a standard rather than the comparison intervention in a clinical trial. We believe that it is reasonable to seek ways to translate this animal research to stroke rehabilitation.[59]

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