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A compact guide to the systematic review and meta-analysis of the literature in neuroscience.

Juliana A Bolzan [1,2], Cilene Lino de Oliveira [1,2].

1- Department of Physiological Sciences, Center of Biological Sciences, Federal University of Santa Catarina – UFSC, Campus Trindade, 88040-900, Florianópolis - SC, Brazil.

2- Post graduation Program in Pharmacology, Center of Biological Sciences, Federal University of Santa Catarina – UFSC, Campus Trindade, 88040-900, Florianópolis - SC, Brazil.

Corresponding author: Prof. Dr. Cilene Lino de Oliveira

Laboratory of Behavioral Neurobiology, Department of Physiological Sciences, Center of Biological Sciences, Federal University of Santa Catarina, University Campus, Trindade, CEP: 88040-900, Florianópolis, SC – Brazil, Phone: +55(48)3721-7085. E-mail: cilene.lino@ufsc.br. ORCID: 0000-0002-0627-530X

Abstract

Critical appraisals of the literature may help to increase reproducibility in neuroscience. Systematic reviews and meta-analyses are tools for neuroscientists to critically evaluate a large amount of knowledge in the research field. These methods involve individually simple decisions, which may become complex when considering the whole process. Strategies to organize the planning and implementation of the protocols minimize the workload. Here, we prepared a compact guide to assist neuroscientists willing to perform a systematic review and meta-analysis of the literature in neuroscience.

Keywords: *Systematic Review; Meta-analysis; Guidelines.*

Introduction

Critical appraisals of comprehensive literature may help neuroscientists to identify more consistent and reproducible findings in the research area. The exponential accumulation of scientific literature prompted methodologies to filter and synthesize evidence (1). Systematic reviews (SR) are transparent and unbiased methods to identify, obtain, filter, appraise, and synthesize studies from the literature to answer a research question (2). Meta-analysis (MAN) is the name given to the pool of statistical methods used to combine quantitative results of different studies into a single one (3, 4). Combining SR with MAN (SRMAN) makes a method to obtain a quantitative synthesis of unbiased information from the literature (5). The SRMAN has been considered the highest level of evidence guiding decision making in Medicine (6, 7), despite the controversies beyond the scope of this text (4). In any case, the synthesis of evidence applied to neuroscience may be helpful to conceive a novel hypothesis or identify gaps in the knowledge about a given subject (8, 9, 10). Moreover, critical appraisal of evidence may optimize future research, minimizing the waste of scientific efforts (11).

Synthesizing evidence often involves labor from teams of reviewers (scientists, methodologists, librarians, statisticians, others) and meticulous preparation to avoid mistakes and biases (12, 13). SRMAN comprises a sequence of individually simple actions. Complexity emerges when considering the whole sequence of steps required to perform SRMAN, while maintaining the quality standards. To guide reviewers through the best practices, the scientific community created guidelines such as “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) and PRISMA-extensions (14, 15, 16). PRISMA provides guidelines to publish results of reviews transparently (14). Guidelines also encourage systematic reviewers to prepare, register, and disseminate protocols before performing a SRMAN (15, 16).

Tools to organize the processes help minimize the workload associated with the planning and execution of a SRMAN. For SRMANs of clinical and observational studies, Cochrane collaboration offers training, instructions, and tools to perform the complete process (https://cccrg.cochrane.org/). For SRMANs of nonclinical or preclinical studies in laboratory animals, free resources may be found at the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE, https://www.radboudumc.nl/en/research/departments/health-evidence/systematic-review-center-for-laboratory-animal-experimentation) or Collaborative Approach to Meta-Analysis and Review of Animal Data of Experimental Studies (CAMARADES, https://www.ed.ac.uk/clinical-brain-sciences/research/camarades/about-camarades). Nonclinical *in vivo, ex vivo,* and *in vitro* studies are

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prevalent in neuroscience, making the frameworks by SYRCLE or CAMARADES more suitable than Cochrane's framework to the synthesis of evidence in this field.

The scientific literature offers excellent manuals providing step-by-step instructions on how to perform a SRMAN in different fields of research (6, 8, 10, 13, 17, 18). For example, Vesterinen (10) made a detailed guide on performing SRMAN of animal studies in the biomedical field. On the other hand, Muka (13) created a simplified guide with 24 steps to perform SRMAN synthesized medical studies. Here, we combined Vesterinen (10) and Muka (13) approaches to provide a simplified, compact guide for neuroscientists wishing to perform a SRMAN for the first time. For this, we organized a flowchart with five consecutive phases of an overview of the complete process involved in a SRMAN (Figure 1): 1- elaboration of a review question; 2- elaboration of a review protocol; 3-protocol preregistration; 4- protocol implementation; 5- review publication. The following text presents a theoretical background for each phase with a brief description and examples taken from neuroscience.

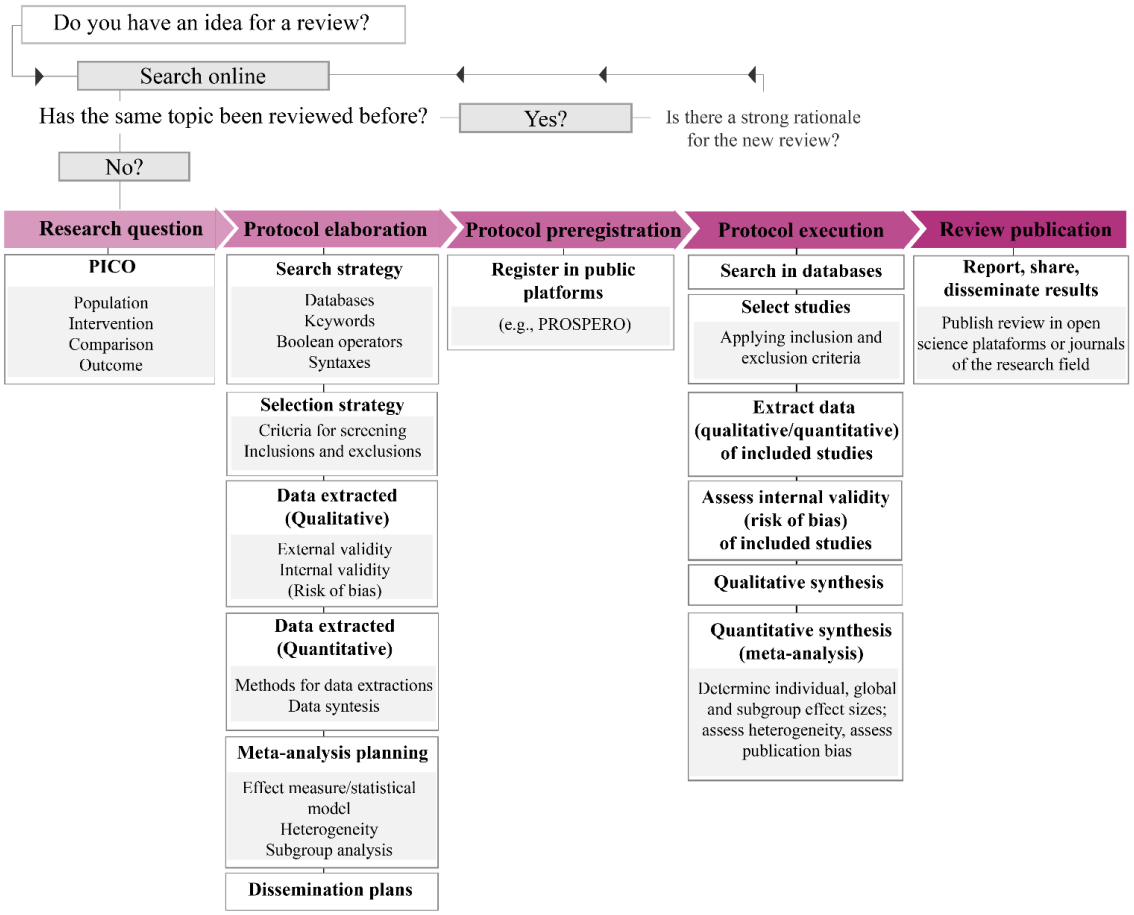

Figure 1. Phases of a systematic review and meta-analysis. The process of systematic review and meta-analysis split into five consecutive phases: 1- review question elaboration; 2- protocol elaboration; 3- protocol preregistration, 4- protocol execution; 5- review publication.

Phase 1: Elaboration of a Review Question

In our opinion, the first, the most crucial phase of a SRMAN is the definition of the research question, which will guide all other steps of the review (19). Neuroscientists are ideal personnel to create a relevant research question to the literature in neuroscience. Before preparing the research question, neuroscientists should scan the literature to check if the same topic has been previously reviewed. When a strong rationale for a review has been found, neuroscientists should elaborate on the review question. Neuroscientists, especially the novice users of systematic reviews, may benefit from the aid of librarians or other methodologists in elaborating a searchable review question.

Searchable research questions may be elaborated using mnemonic tools, helping reviewers remember the components of a well-elaborated, direct, and relevant question to the science field (20, 21, 22). Cochrane collaboration endorses the PICO (P – *Patient* or

population or *problem*; I – *Intervention*; C – *Comparison*; O – *Outcome*) tool when reviewing controlled, randomized, clinical trials (23). Even though neuroscience studies are mostly nonclinical, PICO might be helpful for creating review questions in this field. PICO (Table 1) will be particularly useful to review studies investigating effects of new treatments (e.g., natural or synthetic compounds) or other types of interventions (e.g., toxins, environmental manipulations, etc.) on quantitative outcomes (behavior, neurochemistry, neuroanatomy, etc.) obtained from experimental subjects (human volunteers or laboratory animals are common experimental subjects in neuroscience).

Experimental designs in neuroscience are more variable and flexible than in clinical research (26, 27). Therefore, variations of PICO such as PICOC (PICO plus Context) or PICOT (PICO plus Timeframe) may be helpful (22). Besides PICO and variations, other tools that are potentially useful when reviewing neuroscience literature include SPICE (S – Setting; P – Population; I – Intervention; C – Comparison; E – Evaluation) or SPIDER (S – Sample or population of interest; P – Phenomenon of Interest; D – Design; E – Evaluation; R – Research type). In addition, PICOC, PICOT, SPICE or SPIDER may be handy when specific types of research, such as *in vitro*, *in vivo*, *ex vivo*, or brain imaging is the review's main interest. These last tools may also be suitable when reviewing studies reporting qualitative outcomes (e.g., cell shape or position or color) and contexts influencing the outcomes (e.g., the timing of treatment).

Hence, using mnemonic tools, a complex review question may be stated in more simple, direct terms (e.g., "has the intervention, I, changed the outcome, O, in the population, P, compared to control treatment, C?"). The direction of the expected change of the outcome (decrease or increase) stated in the review question depends on the theoretical background defined by the authors of the question. Based on the experience with the literature in the field, neuroscientists may want to know, for example, "have antidepressants decreased the immobility time of rats measured in the forced swimming test as compared to the vehicle?" (28). Other neuroscientists may ask, "have antidepressants increased hippocampal neurogenesis in laboratory rats as compared to the vehicle?" (29). Moreover, mnemonic tools will help reviewers plan the searches of publications, select relevant studies to answer the review question, and analyze the outcomes.

Table 1: PICO tool: categories, definitions and examples.

Category	Definition	Examples
Population	Population of interest, i.e., biological units receiving the intervention or control treatment from which the outcomes were measured.	*In vivo studies*: volunteers, rats, mice, laboratory animals, *and in vitro studies*: primary cultures, immortalized cell cultures etc.
Intervention	The experimental treatment was applied to the population from which the outcomes were measured.	Chemical treatments (prototypical compounds, new compounds, toxins, so on); environmental manipulations (enriched or impoverished housing for laboratory animals, conditioned media for culture, so on).
Comparison (or Control)	A reference to the effects of the intervention on the population. Standard treatment applied to the population.	Vehicle compared to the chemical treatments; standard environmental conditions (standard housing for laboratory animals, standard media compared for culture, so on) compared to alternative conditions (enriched or impoverished housing for laboratory animals, conditioned media for culture, so on).
Outcome	Measures taken from the population of interest.	Behaviors registered in behavioral tests, protein concentration in samples, number of neurons or glial cells in brain slides, and so on.

Phase 2: Elaboration of a Review Protocol

In phase 2, a protocol is set to annotate the suitable methods to answer the research question elaborated in phase 1. A protocol of a SRMAN may comprise as many as fifty different methodological and analytical decisions, which may lead to different answers to the review question. The extension PRISMA-P (15) was created to help systematic reviewers elaborate a protocol of SRMAN following good practices (http://www.prisma-statement.org/Extensions/Protocols). Decisions range from identifying potential reviewers and collaborators to the results' plans. Templates have been built to guide reviewers through the long series of decisions in a protocol for SRMAN. Cochrane collaboration (30) and SYRCLE (28) offer templates to prepare SRMAN protocols of studies on humans and animals, respectively. Advantages of using a template include preparing a complete plan facilitating the

registration of the protocol in public platforms. Librarians, statisticians, or other methodologists (e.g., experienced reviewers) are essential collaborators for elaborating a SRMAN protocol, especially for the first time.

Besides authors' names, addresses, affiliations, review title, and the review question described in terms of the mnemonic tool, a protocol for SRMAN should contain a brief introduction to the research subject. SRMAN protocols should describe the strategies to obtain the publications from the literature and filter relevant studies to answer the review question. A complete protocol of SRMAN provides the plans for the assessments of internal and external validities, qualitative and quantitative analysis, and the appraisal of the impact of bias on the synthesized evidence (31). A detailed protocol indicates the number of independent reviewers involved in the different steps of the review, how analysis of agreements/disagreements between reviewers and conciliation of disagreements will be performed. Due to the massive amount of information produced during the different steps of a SRMAN, especially in critical activities such as screening processes and data extraction, ideally, two independent reviewers and a third one for conciliation should be involved in each step.

In the following topics, we provide a short description with examples of the items typical of a SRMAN protocol. A hypothetical review question, elaborated using a PICO tool (e.g., "has the intervention, I, changed the outcome, O, in the population, P, compared to control treatment, C?"), is the framework for the examples presented below.

Search strategy: This item consists of a detailed description of how publications will be retrieved from bibliographic bases. Good search strategies are sensitive and specific, usually resulting from small, iterative probes in the bibliographic bases, called pilot studies (18). Pilot studies prevent inadequate retrievals or errors, leading to studies capable of answering the review question. On the other hand, broad and poorly targeted searches can lead to superfluous articles and a loss of time for the reviewers (13). A search strategy should contain the list of search terms (keywords), Boolean operators and syntaxes used in the searches performed in bibliographic databases. Search terms may be chosen with the aid of the same mnemonic tool used to elaborate the review question (Table 2). Boolean operators (e.g., AND, OR) are used to combine the search terms (Table 2). For example, if the targeted population is "laboratory animals", SYRCLE offers filters for a comprehensive search of the literature in Medline and Embase (28, 32). Librarians may provide assistance for advanced searches in different bibliographic bases and reference management. Additionally, bibliographic databases platforms offer updated tutorials on their websites. For example, see examples of protocols presenting search strategies in neuroscience by Ramos-Hryb (33) and Bolzan and Lino de Oliveira (34). Warnings: 1- searches in different bibliographic bases combined will provide a more comprehensive review than one; 2- different search engines operate differently; 3- access to some bibliographic databases require payment or institutional login.

Table 2. Description of a generic search strategy elaborated to obtain relevant publications to answer a hypothetical review question created using the PICO tool:

Search	Search terms	Retrievals (n)
#1	Terms related to (population P or synonyms)	n_p
#2	Terms related to (intervention I or synonyms)	n_i
#3	Terms related to (control C or synonyms)	n_c
#4	Terms related to (outcome O or synonyms)	n_o
#5	Combination of terms used in individual searches, i.e., (population P or synonyms) and (intervention I or synonyms) and (control C or synonyms) and (outcome O or synonyms)	n_{pico}

The search terms field should contain the string of search terms combined by Boolean operators. Every search engine has specific rules to do advanced searches, e.g., some of them require Boolean operators in capital letters, others require specific commands to enter queries, and so on. Therefore, training in search engines is advisable. Reviewers should decide on the adequacy of the search terms to avoid spurious searches (e.g., are keywords related to comparison or controls necessary to obtain relevant studies?). Pilot studies to determine the best search strategy are advisable. The number of publications retrieved in a given search (n) helps to inform about the precision and validity of the searches.

Screening or selection strategy: In this item, reviewers should describe how the relevant studies will be selected among the publications retrieved from bibliographic bases.

The selection or screening process aims to identify the most relevant publications to answer the review question(s) (35). The screening process is easier and unbiased based on the inclusion and exclusion criteria defined beforehand (36). The output of this process will provide lists of references excluded from the review with explicit reasons and a list of studies included in the review. Included studies are the more relevant publications to answer the review question(s) and will be analyzed in the SRMAN (36). The selection strategy includes planning screening phases (title and/or abstract, and/or full text), number of independent reviewers, and conciliators involved. Additional decisions include prioritizing exclusion criteria in the screening phases (e.g., excluding duplicates or reviews in the first phase, i.e., title and/or abstract). The mnemonic tool used to elaborate the review question is helpful to guide the choice of the eligibility criteria (Table 3). For example, criteria related to population (e.g., include if rat; exclude if mice), interventions (e.g., include if tricyclic antidepressants; exclude if all antidepressants except tricyclic), and outcomes are often used in reviews planned using the PICO tool. See examples of protocols presenting screening strategies in the field of neuroscience by Hohls (37), Ramos-Hryb (33), and Bolzan and Lino de Oliveira (34).

Table 3. Description of generic inclusion and exclusion criteria to a screening strategy of studies relevant to answer a hypothetical review question created using the PICO tool.

Category	Inclusion criteria	Exclusion criteria
Population	Studies using population P	Studies using populations a, b or c
Intervention	Studies using intervention I	Studies using interventions a, b or c
Comparison (control)	Studies using control C	Studies using controls a, b or c
Outcome	Studies reporting outcome O	Studies reporting outcomes a, b or c
Type of study	*In vivo* studies	*In vitro* or *ex vivo* studies
Type of publication	Original studies	reviews, systematic reviews, meta-analysis

Reviewers should decide about the adequacy of other relevant categories of eligibility criteria (data, language, experimental design). Exclusion criteria may be more loosely defined than inclusion criteria, e.g., "studies using any population except P" or "studies using any intervention except I" or "studies reporting any comparison/control except C" or "studies reporting any outcome except O"

Assessment of internal validity: In this item, authors should describe the approaches reviewers will use to appraise internal validity, i.e., how well the studies included in the review (primary studies) or the review itself were conducted and reported. There are various tools to assist the reviewer in assessing the methodological quality of the included studies (65, 66, 67). A tool such as RoB-SYRCLE (26), adapted from the RoB tool by Cochrane (38) to animal experimentation, should be more suitable for risk of bias assessment in the field of neuroscience. Although not mandatory in a protocol of SRMAN, the assessment of internal validity of the SRMAN itself may be planned. A tool like the AMSTAR 2, applicable to evaluate the internal quality of systematic reviews, including randomized or non-randomized studies of health interventions (39), may be helpful for the assessment of SRMAN in the field of neuroscience. The number of independent reviewers and conciliators involved in the process should be indicated. The protocol should also provide an analysis of agreements between reviewers (e.g., Cohen Kappa) (40). See an example of a protocol for planning assessment of internal validity of studies in the field of neuroscience at Galindo (41).

Assessment of external validity: This item should describe the approaches planned to appraise the external validity of primary studies, i.e., generalizability, consistency, reproducibility of findings. These evaluations depend on the analysis of qualitative information extracted from primary studies, such as types of experimental designs, population, exposure, or interventions and results. The authors should describe the methods for obtaining these qualitative data, including the number of independent reviewers and conciliators involved in the process, the localization of the information to be extracted (e.g., texts, graphs, tables), and how the authors of the included studies will be contacted to provide missing or additional data. The protocol should also provide an analysis of agreements between reviewers (e.g., Cohen Kappa) (40). Protocols should contain the list of all the qualitative information reviewers decided to extract from the primary studies to evaluate the external validity of the literature in their research fields. Each neuroscientific subfield, or individual review, should decide regarding the relevance of qualitative aspects of the primary studies to evaluate external validity (e.g., species, strain, age, sex of experimental animals or subjects;

type, doses, route of administration, and regimen of drug and vehicle administration; type of measures taken of assays or trials, so on). See examples of protocols planning assessment of external validity of studies in neuroscience at Van Praag (42) and Eckert (43).

Effect sizes estimation: Systematic reviewers often elaborate questions, which the calculation of effect sizes can answer (e.g., how large is the effect of the intervention, I, on the outcome, O, of the population, P, as compared to the control group, C?). Effect sizes are statistics to estimate the difference between groups or the strength of the relationship between variables affecting an outcome (dependent variable) (44). In the fictitious example at the beginning of this item, the calculation of mean differences could indicate how large the difference between the values of the outcome O, measured in the population P, under the influence of treatment I compared to the control C. In other words, the mean difference signifies "the effect of the treatment I on the outcome O". The reviewer should specify the type (dichotomous? continuous?) and the units of measurement of the primary or secondary outcomes according to the protocol to the prespecified review question. Primary outcomes are those essential to answer the review question, while secondary ones are optional. The methods for obtaining the data, number of independent reviewers involved in data extraction, solution of discrepancies or missing information, and tabulation of the data should be planned. The protocol should also analyze agreements between reviewers (e.g., Cohen Kappa) (40). Protocols should also explain how effect sizes will be calculated (e.g., mean difference, odds ratios) using quantitative data extracted from primary studies (e.g., mean, standard deviation, sample sizes, number of comparison, p, F, or t values, correlation indexes, or any other measure, manipulation, or transformation of the data, so on). The choice of the calculations of effect sizes depends on the type of targeted outcome (dichotomous? continuous?), type of study design (controlled? unpaired or paired design?) and comparison of interest (males compared to females? treatment compared to control? before treatment compared to after treatment?). Effect sizes are often estimated and reported, with indicators of uncertainty (confidence intervals, standard error, standard deviation). For a more detailed description of effect size calculations, see Durlak (44). See examples of protocols planning effect sizes estimations of studies in the field of neuroscience at Galindo (41), Soflau (45), and Husain (46) in the “effect measure”.

Meta-analysis: Effect sizes calculated from individual studies may be synthesized or combined in a global MAN or stratified in subgroups. A protocol should specify, per outcome, if a MAN is planned, how the decision of doing it or not will be taken, how estimated effect sizes of primary studies will be combined, and the indicators of the uncertainty of the combined effect size (confidence intervals, standard error, standard deviation, heterogeneity) (47). The number of studies available may be a criterion to decide whether a MAN is feasible or not. Theoretically, two studies are sufficient to calculate a combined effect size. However, as with other statistical methods, a meta-analysis may provide spurious results with small sample sizes (48). Thus, if sample size calculations are planned, the protocol should inform how calculations will be performed (e.g., power analysis). MAN's power analysis may be performed using the Metapower package in R (49). In the case of a feasible MAN, the reviewer must pre-specify the statistical model of analysis (e.g., random effects or fixed effect model); the statistical methods used to evaluate heterogeneity (e.g., I^2, Q); subgroup analyses; sensitivity analyses and evaluation of publication bias. The decision on a suitable statistical analysis model depends on the degree of heterogeneity anticipated for the MAN (50). Random effect models are often eligible to MAN in research fields like neuroscience, in which a variety of study designs are often employed to investigate a similar research question. A high degree of heterogeneity may also justify the planning of the subgroup analyses (51). Relevant subgroups explaining the variability of data are dependent on the research field, and authors may stratify the MAN into subgroups according to the categories selected for external validity assessment (e.g., features of population, intervention, control or outcomes). For example, in animal studies, the species, strain, age or sex of laboratory animals are expected to affect the results of a study. If the assessment of publication bias is planned, it should be also included in the protocol. Publication bias, prevalent in basic research (52), may be assessed using the trim-and-fill analysis and funnel plotting method (53, 54). The complexity of the study design may sometimes require calculations beyond classical MAN methods such as network MAN, for example, Dias and Caldwell (55). See examples of protocols describing plans for MAN in the field of neuroscience at Pozza (56), Galindo (41) and Santos (57) in the “strategy for data synthesis”.

Dissemination plans: Planning for disseminating the results comprises part of the review process and should be prespecified, even vaguely, in the protocol to accommodate the expectations of all the authors involved. Systematic reviews often involve large groups of reviewers and authors should decide how all contributors will get the credit. Some periodicals permit the use of group names (e.g., The NPQIP Collaborative group, (58)), while others may request the list with all contributors. It is up to the authors to identify the appropriate media to make the results available to the appropriate public. See examples of protocols describing dissemination plans in the field of neuroscience at Álvarez-Bueno (59) or Bolzan and Lino de Oliveira (34).

Phase 3: Protocol Registration

Preregistering the protocol is recommended to avoid overlaps and superfluous efforts and to encourage the rigor and transparency of studies (13, 15, 27). Protocol registration before starting to perform the SRMAN may help reviewers stick to the plan, as a long list of decisions needs to be made over the process, reducing the incidence of biased reviews. Furthermore, transparent dissemination of the protocols may attract collaborators to join the group of reviewers, which may be beneficial to perform the plan, especially when handling many publications and studies.

PROSPERO is a public platform specialized in registrations of protocols for SRMAN of studies relevant to human health in humans or laboratory animals (https://www.crd.york.ac.uk/prospero/). Currently, rapid reviews and umbrella reviews, not scoping reviews, are also eligible for PROSPERO registration. The Open Science Framework (OSF, https://osf.io/) is also a public and free of charge platform used to deposit scientific protocols of any study, including SRMAN protocols. Protocols may also be published in scientific journals with peer review (e.g., 33, 34).

Phase 4: Protocol Implementation

Phase 4 comprises the implementation of all decisions included in the protocol created (phase 2) and preregistered (phase 3) beforehand. Although time-consuming, protocol implementation may be less complex than protocol elaboration. In our experience, most of the actions involved in searching publications and selecting studies using pre-established rules can be quickly learned by inexperienced reviewers. The extraction of data (quantitative and qualitative) from included studies is the most time-consuming step of a SRMAN and can be challenging, especially for inexperienced systematic reviewers (11). Applying the pre-established analytical choices are technically simpler than planning a MAN due to the availability of intuitive tools and software (e.g., 60). Perhaps procedures to guarantee data integrity and tracking the process are the most considerable challenges in this phase; thus, inexperienced systematic reviewers will benefit from interaction with more experienced collaborators. Ideally, deviation of the protocol during implementation should be annotated to be presented in the final report. A public platform like OSF (https://osf.io/) may be a valuable resource for reviewers to keep track of all documents created in the process of a SRMAN.

There are many different free or commercial resources available to implement the processes in a SRMAN; degrees of automatization vary from step to step. For example, the metagear package for R is a free resource facilitating screening, data extraction, and MAN (61). Packages for R such as metagear (61) or pacman (62) may be used to calculate the agreement between reviewers (Cohen Kappa) (40) whenever two independent reviewers performed an activity (e.g., screening process, data extraction, and so on). In the following text, we make suggestions of selected free resources to implement each step of a SRMAN in any field of nonclinical research, including neurosciences:

Searching publications, deduplication: The "advanced search" menu of search engines (e.g., Pubmed, Web of Science, Embase, Scopus) are often more appropriate for the type of search required in a systematic review than the simple search menu. Recovering documents from different virtual bases requires reference management software for deduplication (63). Mendeley (https://www.mendeley.com/download-reference-manager/), Zotero (https://www.zotero.org/) and Rayyan (64) are examples of free managers. CAMARADES developed a web application for deduplication (Automated Systematic Search Deduplication Tool, ASySD, https://www.ed.ac.uk/clinical-brain-sciences/research/camarades/tools-resources). The number of publications obtained in the searches performed in every bibliographic database, before and after deduplication, should be annotated in the final report.

Screening relevant studies: Reference management software is handy to apply the

selection criteria (63). Mendeley (https://www.mendeley.com/download-reference-manager/) and Rayyan (64) can be used to classify references in a library semi-automatically. Rayyan supports the initial screening of abstracts and titles using a semi-automation process while incorporating a high level of usability (63, 64, 66). Other free resources are ASReview (https://asreview.nl/), Parsival (https://parsif.al/), Rvtools (tools for evidence synthesis in R, https://revtools.net/), Sysrev (https://sysrev.com/), "Screenatron and Systematic Review Accelerator" (66), SyRF (https://syrf.org.uk/ , CAMARADES). All these software allow for multiple reviewers' assessment facilitating independent judgments and conciliations. Results of screening processes (number of excluded studies, reasons of exclusion, number of included studies) should be annotated to be presented in the final report.

Data extraction for internal or external validity assessment and effect size estimations: Assessments of internal or external validities require information extracted from the text of primary studies. Various software applications support extracting text from PDF, including free trials of proprietary software (PDF readers). The reference managers themselves can be helpful to obtain bibliographic information (e.g., authors' name, year, journal, so on). CAMARADES are developing approaches to automate data extraction to facilitate the application of the RoB-SYRCLE tool (67). Reviewers interested in applying to AMSTAR 2 may find a helpful checklist available at: https://amstar.ca/index.php. Online tools such as Colandr (https://colandrcommunity.com/, Colandr Community), Systematic Review Data Repository (SRDR) or SyRF (https://syrf.org.uk/, CAMARADES) enable efficient form for annotating, building, sharing, and data management (68). Although most of the above-mentioned online tools cannot automatically extract data from primary publications, they allow for multiple reviewers' assessments facilitating independent judgments and conciliations. Tabulation of extracted information provides a database that will facilitate MAN, data sharing and the final report.

Data extraction for the effect sizes estimation, meta-analysis calculations and plots: In the field of neuroscience, most of the quantitative data from primary studies are in graphs and/or tables. Although time-consuming, manual measurements of scaling or bar sizes, line extensions, and other graphical attributes are accessible using the digital ruler (e.g., free Adobe Reader). Some knowledge of the programming language allows using the R metaDigitise package to extract descriptive statistics such as means, standard deviations, correlations automatically from different chart types (box, scatter, histograms) (69). Tabulation of the extracted information provides a database that may facilitate MAN, data sharing and final report. Software specific for MAN will provide the values of effect sizes with confidence intervals of primary studies, the combined effect size along with measures of uncertainty (e.g., confidence intervals, standard error), heterogeneity and plots [70, 71]. Tools such as Meta-Essentials (https://www.erim.eur.nl/research-support/meta-essentials/ (60), RevMan (72) or OpenMEE (73) can be used by reviewers unfamiliar with statistical software or programming language in conducting MAN (74, 75). Reviewers more familiar with coding can benefit from software such as meta or Metafor packages in R (74); Python or OpenMeta [Analyst] (60). Information about software and packages selected for data extraction and MAN should be annotated to the final report.

Phase 5: Review Publication

A transparent report may help readers appraise the reliability and validity of the results of the SRMAN and other neuroscientists to reproduce the study. PRISMA Statement has developed several extensions to facilitate reporting different types or aspects of systematic reviews (http://www.prisma-statement.org/Extensions/). Reviewers may adopt different strategies to publish, share and disseminate results of the review, including scientific events, workshops or online platforms and peer-reviewed journals (several available). In peer-reviewed journals, unless otherwise specified, the report of SRMAN may be organized like other types of publications, including an introduction to the subject, methods, results, and discussion (76, 77, 78, 79, 80). The report of a SRMAN may also be a part of a narrative review (29). Some journals request that articles report a SRMAN to submit a completed PRISMA checklist, available at www.prisma-statement.org or journal websites to facilitate the peer-review process.

The **Introduction** of an article reporting a SRMAN contains the theoretical background, hypothesis, and the review question stated using the terms of the mnemonic tool. Methods may

be briefly presented, primarily when the reviewers can provide the reference or identification number of the preregistered protocol (e.g., PROSPERO number or a link of OSF). The **Methods** section could be divided into subsections describing the search strategy, screening strategy, data extraction, quality assessments and analysis. Detailed descriptions of the search and screening strategies are pivotal to replicating the review but are frequently too extensive to be presented in an article. Short versions of the search and screening strategies may be presented in the Methods along with the reference or link to access the detailed strategies (e.g., a link of OSF). Reporting the date of the searches is always crucial because the number of publications retrieved may change over time. The methods used to extract the qualitative and quantitative data from the primary studies should be presented. Approaches selected to assess internal and external validity should be mentioned and described. Important: calculations and interpretations of effect sizes should be explicitly stated because they have an impact on the discussion of data. A description of the analytical choices of the quantitative analysis, with or without a MAN, should be presented in the Methods section, even when the preregistered protocol is cited.

The **Results** section may be divided into subsections describing the output of the search and screening strategies, quality assessments of the included studies and, finally, meta-analysis. The number of studies retrieved in each bibliographic database, excluded by exclusion criterion, fulfilling inclusion criteria, included in the qualitative analysis, and included in the quantitative analysis should be reported and also in a PRISMA flowchart (36) presented as a Figure in the manuscript. Results of the RoB assessment may be presented as tables or charts. For example, the plot for RoB-Syrcle may be performed using the Robvis R package (81). Qualities of the individual studies may be reported in the text or tables. Global or subgroups meta-analysis results are often presented in a Forest plot (82), enabling the appraisal of individual and combined effect sizes in a single figure. Scatter plots are standard, especially when meta-regressions are reported (83). Funnel plots (84, 85) are especially recommended when publication bias assessment is reported. A link (e.g., link of OSF) containing files with raw data will help readers appraise the results' quality.

The **Discussion** involves the examination of the internal and external validities of the publications included in the review, which is valuable for the appraisal of the quality of the data available in the research field. Results of the MAN should be discussed in terms of direction, magnitude, the significance of individual and combined effect sizes. The direction of the effect size, i.e., positive or negative values, usually indicate evidence, respectively, in favor of or against an intervention or treatment or exposure of interest (warning: positive or negative signals of effect size have no absolute meaning depending on the type of calculation performed, e.g., subtracting low value means from high-value means will give a negative effect size). In neuroscience, the benchmarks to interpret the magnitude and significance of the effect sizes are yet to be established. In other fields of research, effect sizes have been classified from small to very large (86, 87), while confidence intervals excluding null may be considered "statistically significant" (88).

Publication bias, prevalent in basic research, often inflates combined effect sizes, distorting the evidence's appraisal (89, 90). The impact of heterogeneity on the combined effect size should be addressed. In the field of neuroscience, features of the population (e.g., species, strain, age, sex), intervention (dose of the drug, via of administration), types of control groups or types of outcomes may have an impact on results of the studies. Authors may discuss how stable the effect sizes were across subgroups. In the conclusions, authors may summarize how reliable the review results are according to the internal and external validities assessments. Additionally, authors may elaborate on how heterogeneity and publication bias may be affecting the conclusions of the review. Finally, limitations of the review process might be disclosed.

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