Rationality and Novelty of Instrumental Use in Neuropsychological Research Evaluations: Taking Infinity to Singularity

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***Abstract*— Background: Few studies address the rationality of utilization of instrumental tasking and maze learning in neuropsychological research evaluations; this is apparent from the literature search in biomedical databases with appropriate keywords yielding nil hits for rationality of such usage. Furthermore, how could such rationality be interpreted and used for scientific benefits of the researcher? What is the scope of applicability of such research in neuropsychology to patient care? This systematic review addresses such key issues and focuses on ways to appraise such research articles using rationality as the key criterion in such appraisals and interpretations.**

Objectives & scope: The systematic review focuses on deciphering the rationality and novelty of instrumental usage in neuropsychological research and patient care, from a thorough literature search in a seven month period from January 2013 to July 2013 in the "medline" database. The review was a pilot initiative to give a recommended harmonized validated checklist to best search, select, appraise, and apply such research for two purposes – psychological research and patient care.

Methods: To this end, this meta-analysis uses "medline" index and "pubmed" database to establish a list of the pre-clinical and clinical research articles using instrumental tasks and maze learning in the last seven months. Then, quantitative analysis of these included articles are performed using MS Excel 2013 with Daniel XL-add in. Qualitative analysis of the selected articles has been performed using a pilot checklist validation, provided in this article; the same can be used for appraising and applying such research to the benefits of researcher and patients. The last seven months has been chosen appropriately since this is a pilot attempt to fulfilling the objective that it intends to do so.

Conclusions & limitations: This meta-analysis will be useful in giving recommendation about how to select and critically appraise and interpret such neuropsychological evaluations in research using maze and neurological instrumentation. The study has not considered in-depth the methodologies of each individual research study. Although novelty was one of the objectives, it could not be met with appropriately due to the diverse nature of methodologies followed in each of the included research articles. Nonetheless, this pilot meta-analysis must encourage more explorations in this research area from a broader perspective in the future.

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***Index Terms*—maze, cognition, memory, learning, behavioral assessment, Exteroceptive cognitive models, procedural memory, research appraisal, behavioral metaanalysis**

I. Introduction

Mazes and similar instruments have been in use for psychological evaluations in rodents for a long time. In recent times, they are even being used to study neurological and biochemical bases of cognitive processes in animals, and even in clinical neuropsychiatric studies in human participants and patients. They are also used along with other invasive research endpoints in psychology, and non-psychological or pseudo-psychological markers and surrogate endpoints. The probable advantages in their increasing usage in research, either alone or in combination with other disease markers, may be due to their sound accuracy as surrogate markers of cognitive processes and also being minimally invasive and even non-invasive, such instruments offer ethical advantages.

The earliest use of such instruments dates back to 1898 when Thorndike constructed a problem box that helped an animal subject to learn by manipulating a door button or similar object at its control. This was then followed by Small (1899, 1900) who devised a maze, essentially a reproduction of the Hampton Court maze, to help an animal subject learn a fairly complex path. Now, the availability of such mazes make such learning behavior and evaluations easier. In spite of their abundance and complexity, mazes constitute only a group of many such instruments used in research, but the complexity of their designs and simple yet very effective means with which the experimenter variables kept somewhat constant, the subject variables altered to the needs of the experimental design, make them an indispensable tool in research. Still, the variety of techniques and procedures for varying subject variables and the complexity of some of such protocols make them difficult to rationalize and standardize based on the specific cognitive domains that they are used to elucidate. For example, the y-maze is commonly used to elucidate novelty recognition in only one of the procedures, but in other protocols it is used to study discrimination learning, long term memory and even reward behavior. In each of such evaluations, there may be only minor change in its design, but even this is may be

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sufficient to change the cognitive domain studied. Then, how do we rationalize such usage of instruments and procedures in order to standardize their appropriateness to psychological processes? It makes such a task difficult for psychologists, but is a mandatory need even in modern proteomic era, but of the versatility in using such instruments in research: almost making infinite such possibilities approach near unity! This is supported by the fact that using 'MeSH' keywords "maze" under a last thirty year limit to search for such research in NCBI's "pubmed" database ("medline" index) yields twenty three thousand one hundred and ninety six articles in "pubmed" database, compared to twenty four thousand three hundred and ten, without that thirty year limit. This is an important fact that such articles involving such instruments, alone or combined with other markers / methods of assessment, are important even in this post-genomic, peri-proteomic era.

Hence, this metaanalysis is a subtle attempt at such a rationalization, though a small one. At the end of this review, the reader will be appreciate the various procedures and instruments used in evaluation of cognitive and neuro-psychological processes, both pre-clinical and clinical, especially maze learning.

II. META-ANALYTIC METHODOLOGY

Prior ethical approval (IHEC proposal number: 13/185) was obtained for this study from a SIDCER-recognized Institutional Human Ethics Committee in PSG Institute of Medical Sciences & Research, India.

The author used the US-NCBI's "pubmed" (www.ncbi.nlm.nih.gov/) database to search for articles with NLM's 'MeSH' ('Medical Subject Headlings') keyword "maze" and limits "01/01/1983 to 31/07/2013" and "free full text" to obtain a series of pre-clinical and human research articles pertaining to but not exclusive of mazes. The last thirty year period was chosen to reflect the importance and abundance of such research even in the genomic and proteomic era. Each article was analyzed and studied to deduce the instrument used, parameters evaluated, cognitive domain studied and the model (animal species or strain or human) assessed. The current meta-analysis is an initial step in this literature search in that it included such research published in this database only in the first half of this year, totally eighteen articles. The two criteria used in article selection-cum-analysis were rationality and novelty in assessment of the cognitive domains that they were meant for in this seven month period in 2013. The author has not noted any potential source of bias in the studies considered in this meta-analysis.

The following checklist summarizes the methods undertaken in the meta-analysis (Diagram 1):

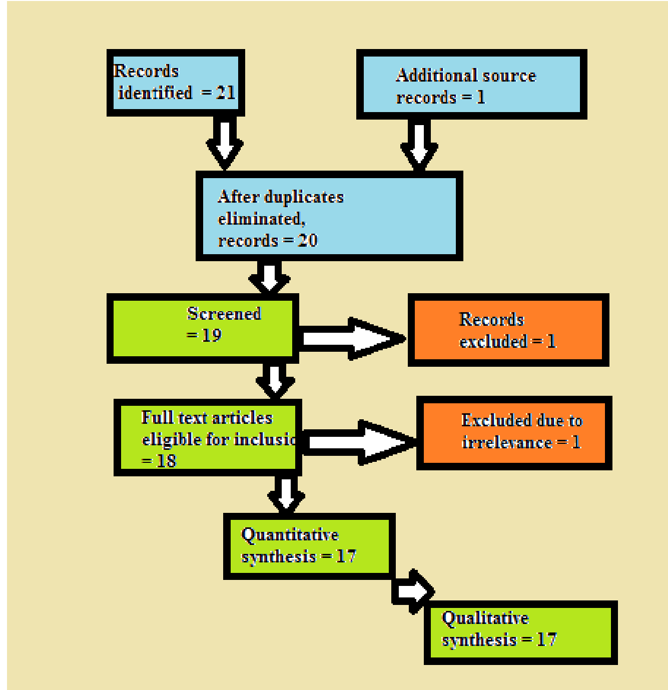

Diagram 1: Adapted PRISMA checklist depicting the key methodologies followed in the conduct and synthesis of this meta-analysis.

This study used basic statistical data tabulation, compilation, and analysis, than that for a more formal, full-fledged meta-analytic studies due to the few sample studies included and limits posed by the area of meta-analysis.

Finally a format checklist for selection, clinical applicability, reproducibility, and appraisal of such research articles has been provided as a modest recommendation – only as a preliminary guideline that can be imposed upon by the readers, if required. A limitation would be the lack of consideration of methodologies used by each study in detail, but omitted due to intention to be simple in the interpretation of these studies.

III. RESULTS

A total of twenty original research articles were analyzed for the rationality and novelty in the use of instruments in their research and the related procedural protocols. Cross-references and supplementary data files to these articles, if available, were also thoroughly scrutinized for their rationality and novelty – one article was excluded based on these criteria. A summary of those pre-clinical studies and the various parameters and domains studied to assess neurological functions is provided in Table 1:

INSTRUMENT	NEUROLOGICAL DOMAIN	REFERENCES
Activity cage	Motor activity	Quierez, et al., 2013
Open field box	LTM*, Novelty recognition memory; anxiety; social interaction	Cui, et al., 2013; Botha, et al., 2012; Ohira, et al., 2013
Operant testing chamber	LTM*, Contextual fear conditioning	Ciu, et al., 2013
Startle reflex measurement system	Prepulse inhibition (Schizophrenia)	Ohira, et al., 2013
Porsolt Forced Swim Test	Depressant activity	Ohira, et al., 2013; Kumar, et al., 2012
Tail suspension test	Neuromuscular strength	Ohira, et al., 2013
Stair case test	Activity & exploration	Katzav, et al., 2013
Rota rod test	Motor coordination & Balance	Ohira, et al., 2013
Hot plate apparatus	Algesic sensitivity	Ohira, et al., 2013

Table 1: Non-maze Instrumental tasks used as surrogates to evaluate various neurological functions in lower animal models. (*LTM = Long Term Memory)

The following table condenses the mazes and cognitive domains that they were measuring used in various pre-clinical models in this seven month period (Table 2):

MAZE	COGNITIVE DOMAIN	REFERENCES
Cheeseboard maze	Spatial memory	Dupret, et al., 2013
Vertical T-maze	Olfactory learning	Stelinski, at al., 2013
Morris water maze	Spatial discrimination learning, spatial learning	Han, et al., 2013; Xu, et al., 2013; Taghizadeh, at al., 2012
	Spatial reference memory, working memory	Zhang et al., 2013
	Temporal recognition memory	Botha, et al., 2012
Marlau maze	Navigational spatial memory	Fares, et al., 2013
	Anxiety	
	Exploration	
	Cognitive stimulation & social interaction	
Elevated plus maze	Anxiety	Quieroz, et al., 2013; Ciu, et al., 2013; Botha, et al., 2012; Katzav, et al., 2013; Kumar, et al., 2012
Water plus maze	Spatial reference memory	Ciu, et al., 2013
Horizontal t-maze	Working memory	Ohira, et al., 2013
Elevated t-maze	Anxiety	Kumar, et al., 2012
Swim t-maze	Learning	Katzav, et al., 2013
y-maze	Exploration, Spatial reference memory	Kivity, et al., 2013; Ohira, et al., 2013
Elevated linear track maze	Spatial experience-based learning, novelty learning	Dragoi, et al., 2013

Table 2: Maze procedures as surrogates used to evaluate higher cognitive domains in animal models. The Marlau maze is a patented and engineered maze whose design can be altered to suite the domain studied.

The following table summarizes the tasks used to study human cognitive processes (Table 3):

TASK	COGNITIVE PROCESS	REFERENCE
Simple reaction task	Reaction time	Konagai, et al., 2013
Groton maze learning	Spatial learning	
2-back paradigm	Working memory	

Table 3: Tasks used as surrogates to evaluate human cognitive processes.

As is evident from Figure 1, mazes were the commonly used instruments used for psychological research, followed by other apparatus and non-maze devices and lastly, by human tasks. Spatial memory and anxiety, score as maximum-in-extent studied neurocognitive domains studied, corresponding to mazes and non-maze instruments.

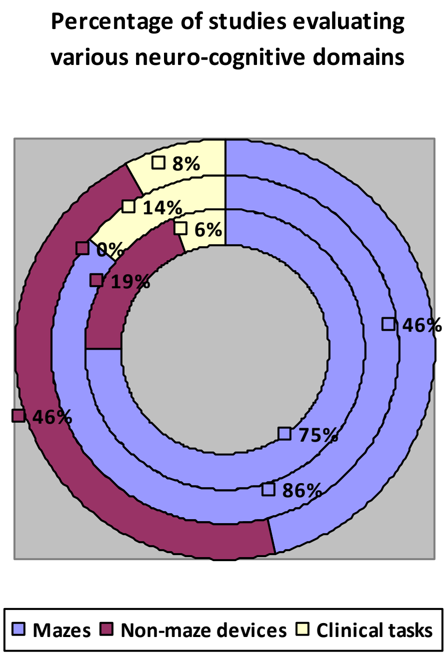

Fig. 1: Doughnut Chart showing the relative percentage of studies in last 7 months, evaluating various neuro-cognitive functions viz. memory, learning, neurological (as three concentric doughnuts, in that order, from inside out), in each functional evaluation, the use of mazes and non-maze instruments, and clinical tasks is denoted in that order by each of the color coding. (% values correspond to the total number of studies as 100 %]

Of all cognitive functions evaluated, spatial memory comprises the majority, followed by working memory; in sensory-motor function evaluations, anxiety (anxiolytic / anxiogenic) forms the chunk of the total such functions assessed.

The following figures summarizes the various functions assessed and evaluated in these studies (Figure 2, 3):

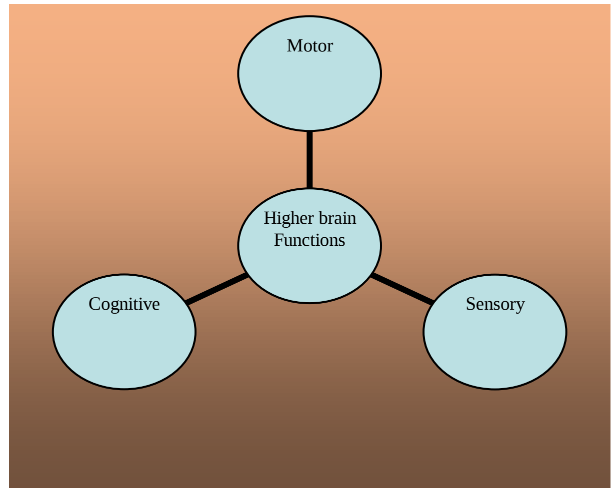

Fig. 2: Functional classification of basic central nervous system functions that contribute to higher functions like intelligence and problem solving. Each class comprises many more functional groups.

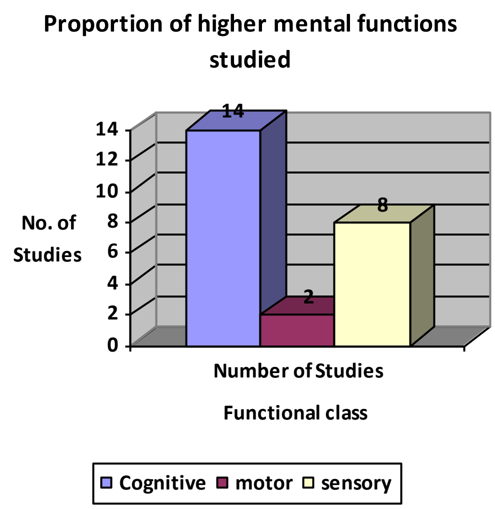

Fig. 3: Bar Chart depicting the proportion of studies evaluation each class of mental function to total number of studies (as 18). Values at the top of each bar denote absolute number of studies.

Almost all these studies had employed novel methodologies, the use of which must be encouraged in psychological research utilizing mazes and other such useful instruments. This is apparent from the use of genetic and recombinant animal (rodent) models in many of these studies (Figure 4).

As would be inferred from figure 4, the rat is the most commonly used model in these eighteen studies, followed by mouse and other models. Although the zebra fish is a versatile model in psychology its use is practically zero in the last seven-eight months, an important finding in this meta-analysis. Its use must be encouraged and recommended in such research if technical feasibilities allow its use. Similar principles hold true for drosophila models. Infact, principles of alternatives to animal research – 3Rs (Reduction, Replacement & Refinement) recommend such alternatives to animal usage, if not wastage, in all types of research protocols!

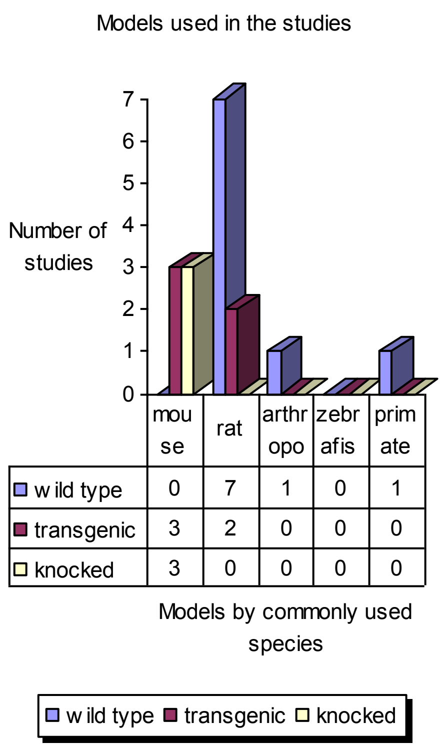

Fig. 4 bar chart denoting a plot of various animals used as Interoceptive models, along with categories of each model type, from presumably most commonly useful species to those least used in psychological research: mouse → rat → arthropod (inc. drosophila) → zebra fish → human; Z-axis shows the number of studies using each model.

This metaanalysis is limited in the fact that the methodology followed in each article have not been appraised and assessed, and the study sample chosen is too small to come to cutting-edge conclusions. Yet, it may well have served the purpose of a pilot metaanalysis, if it fueled interest in the readers to properly and rationally chose a research involved in psychological instrumentation, and carefully and accurately assess its novelty and appropriateness, especially its relevance to the ultimate application targets, the patients.

The following table (Table 4) summarize the scientific research areas that these studies have explored into:

FIELD EXPLORED	DISORDER / THEME INVESTIGATED	NO. OF STUDIES
Molecular neurosciences	Hippocampal interneuron circuits in spatial memory	3
	SNAP 25 protein mutations in cognition	
	Neurotransmitter receptor* mutations in Long term depression (LTD)	
Neuro physiology	Odorant response model development	3
	Developmental stress, exercise & memory	
	Spatial experiences in rats	
Molecular pathology	Estrogen receptors in cognition	4
	Metabolic syndrome	
	Lupus syndrome	
	Anti-phospholipid syndrome	
Neuro pharmacology	Statin in Alzheimer's disease (AD) model	2
	Pioglitazone in AD model	
Nutrition	Epilepsy	3
	Chicken extract & memory (human study)	
	Vitamin D deficiency	
Infections & behavior	Toxocara / Toxoplasma (organisms, usually causing opportunistic infections in humans) & memory	1
Alternative medicine & reverse pharmacology	Plant extract (as part of Chinese medicine) & anxiety, memory endpoints	1
	TOTAL	17

Table 4: Summary of field of investigations of the seventeen original research studies considered for meta-analysis. [NR2A/2B = neurotransmitter receptor subunits for NMDA, N-methyl D-Aspartate].

The following figure (Fig. 4) summarizes the classification of psychological models in research:

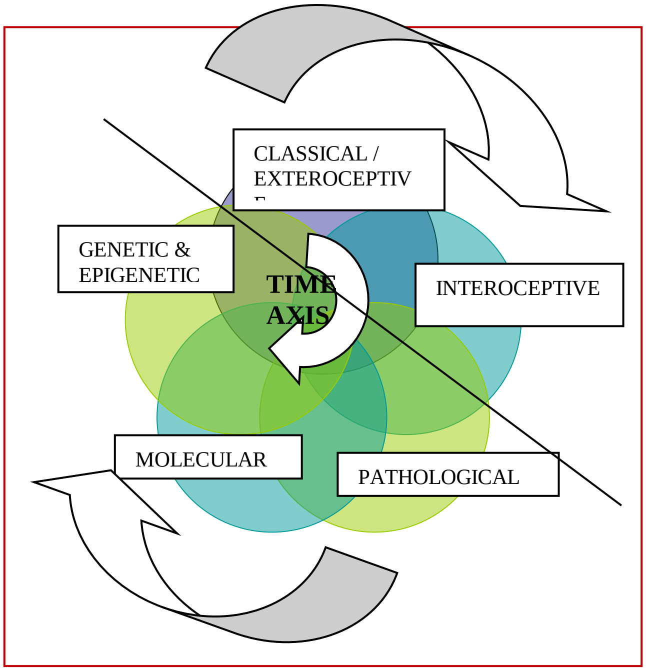

Fig. 5: Psychological research approaches – their timeline, and characteristics. Characteristics are based on simplicity of approach, invasiveness either in animals or in human subjects, and efficiency of the approach w.r.t. the yield of results.

The above diagram (Fig 5) shows that in recent times, more mechanistic and complex approaches have been devised in neuropsychological research. As will be apparent, these must be combined with basic and minimally invasive approaches in future research methodologies in novel permutations and combinations to increase the efficiency of the yield. As a word, this can be applied to various fields to decipher not only complex hypotheses of research undertaken, but also to understand the still-mysterious but a basic process of brain function viz. cognition.

IV. DISCUSSION

Researchers have evaluated the influence of developmental stress in rats on anxiety in elevated plus maze and open field box, and temporal recognition memory in Morris water maze. [8] Although such evaluations have been carried out often, these instruments are narrow in the specific context undertaken and broad in the process they evaluate. To reduce this limitation, a powerful combination of genotypic and molecular methods must be made along with such phenotypic models to increase the scope of research and applicability. To illustrate this statement, Cui, Z., et al., have employed diverse models like open field box, elevated plus maze, hidden platform water maze along with operant testing chamber, along with molecular methods to evaluate long term depression, a base for long term memory, in transgenic rodent models recently.[9] This can be employed in physiological [10, 11, 12], natural, [17] environmental, [13, 14] nutritional, [21, 25] or pathological models.[15, 16, 18, 19, 20, 22, 23, 24, 26]

Memory and learning experiments form a large portion of those undertaken and evaluated by psychologists, although they comprise a subset of yet-underdetermined and bizarre cognitive processes. Memory has been extensively studied and its neurological base has been known, though less determinatively. Human memory has two counterpart origins, the cortical and subcortical. The thalamic nuclei may be a third base of memory process origination, especially that for emotional and fear related memory. It is of significance in human disorders ranging from alcohol addiction to dementia. Human learning has always intrigued researchers, but its implications and relevance are almost infinite – it is one of the bases of psychotherapy and psychiatric counselling.

Spatial memory may be the most commonly affected facet of memory, especially its long term component. It is ubiquitous in its presence both in procedural and declarative memory, much like auditory memory. But it is easier to evaluate visuo-spatial memory than auditory memory both in animals and humans alike because of the quick and more effective means of learning from visual cues and easy accessibility in the former, and the presence of less subjective bias than auditory memory, in the latter.

Working memory is perhaps the most commonly affected memory process in human disease. It is commonly affected even in human patients with diseases that have a small psychological base, for example, diabetes mellitus. Hence, it may be more prudent and worthwhile to assess working memory than any other form of memory in human and animal experiments. Yet, it may be difficult to design and interpret an animal experiment based on working memory disorder patterns in human disorders.

Auditory memory may be impaired in human patients, but it may be difficult to conceive this effect in experiments, as is apparent from the results of this meta-analysis. This rule will hold true for olfactory learning and other less accessible compartments of memory in relation to the experimental design alike.

To note is the fact that of the eighteen research articles reviewed here, one human study has claims of evaluating the reaction time, this may be a better option to study in humans, but confounders like the speed of reflexes, tone of muscles, and others may be involved in evaluating reaction times involving motor functions.

In using non-maze instrumental parameters, anxiety and depression may have been over-emphasized and evaluated much more than required in these studies, though easier to study in animal models, may not hold true in human diseases as such evaluations, especially in rodent models, are more specific and therefore, less sensitive.

V. RECOMMENDATIONS

A set of following criteria may be used to appraise a neuropsychological research article involving mazes and similar instruments, and critically apply it to human disease:

1. Is the study relevant to humans (applies to both pre-clinical and human studies)? What function of brain does it propose to evaluate and assess?
    a. If yes, will the study be useful in treating human disorders?
    b. If no, will the study be theoretically be helpful in advancing psychology?
2. If yes to 1 (a) above, what kind of human disease will it be useful in its contribution – those with a psychological basis / a neurological base / others with cognitive derangements, but without any of these bases? Consider:
    a. Extrapolation practicability to humans
    b. Difficulties faced in extrapolation from animal models to human patients / subjects / participants
    c. What cannot be applied to humans?
3. If no to 1 (a) above, what area and branch of psychology will it help in scientific advancement?
    a. Biopsychology?
    b. Behavioral & Cognitive psychology?
    c. Neuropsychology?
    d. Clinical psychology & Psycho (somatic) therapy?
    e. Psychiatry / neuropsychiatry?
    f. Neurology?
    g. Other areas?
4. Does the study have novelty in its design / methodology?
    a. If yes, what is the lacunae it fills up with this novelty?
    b. Can this study design be the only rationale one to study the brain functions evaluated?
5. Is the animal model / human task chosen rationally?
    a. Is it a sole Exteroceptive model?
    b. Does it use a combined Exteroceptive and Interoceptive evaluations?
6. If it is all relevant, novel, and rational, can it be reproduced in other (even your) laboratory in similar conditions? Will it help your patients too?
    a. Is it cost effective?
    b. Is it ethically sound in using Interoceptive models? If not, what could have been done to minimize harm to animals – Reduction / Replacement / Refinement / Rehabilitation?
    c. Can the results of Exteroceptive model evaluations be applicable to *your* practical benefits?
    d. What would be the advantages and limitations of these methods?

The above list of criteria can be scored as per requirements to choose and interpret a neuropsychological research during any literature search in a biomedical or scientific literature database. It may be stressed that this list may even comprise only a subset of actual criteria for appraising a neuro-psychological research article. This may be used with guidelines available for reporting in-vivo and human studies like ARRIVE[2] and components of EQUATOR network like CONSORT[3].

This metaanalysis would not meet the author's expectations if it merely stopped at making complex neuropsychological research (infinity) simpler (singularity) – rather this singularity must be taken again to infinite other novel but rational neuropsychological research methodologies using this as a cue!!!

V. DISCLAIMER & CONFLICTS OF INTERESTS

The author acknowledges absence of any financial and / or non-financial conflict(s) of interest(s) with any person or agency involved directly and indirectly in the conduct of this metaanalysis. Further, the author declares the originality of this metaanalysis, and that it has not been essentially a duplicate of research work carried out elsewhere, to the best of his professional competency.

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