Administrative information

Title

The mirror mechanism in schizophrenia spectrum disorders: Protocol for a systematic review and meta-synthesis

Registration

To be registered in PROSPERO. A protocol reported in line with the PRISMA-P statement (1).

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Contributions

AV is the leading author for protocol development, analyses, and dissemination. AV is also the first reviewer and the corresponding author. All authors will contribute to data interpretation and article drafts.

Amendments

Important protocol amendments post registration will be recorded and included in dissemination.

Support

No sources of support or funding were provided for this review.

Conflicts of interest

All authors declare there are no conflicts of interest regarding this study or its possible results.

Introduction

Rationale

Schizophrenia is one of the most debilitating and common neuropsychiatric disorders in the world, with an estimated incidence of 1% in the population worldwide (2). Deficits in a variety of cognitive domains are well-known for this disorder (3-5) and they are listed as specifiers for schizophrenia in the 11th revision of the International Classification of Diseases (ICD) (6). One of the cognitive domains of controversy in schizophrenia is Motor Resonance, also known as the Mirror Neuron System (MNS). Mirror neurons are visuomotor neurons that perform mirror mechanisms, meaning each time an individual observes another individual performing an action, these neurons which encode that action, are activated in the observer's cortical motor system (7, 8). These neurons were first discovered in the premotor area F5 of macaque monkeys (9-12). Later, similar neurons were found in the inferior parietal lobule, area PF, of macaque monkeys and the concept of 'mirror system' was established. Since the discovery of mirror neurons, some studies have claimed the discovery of similar neurons in various regions of the human brain, including the ventral premotor cortex (13, 14), inferior frontal gyrus (15-19), and inferior parietal lobule (14, 20). Meta-analyses of fMRI studies have demonstrated that there might be other brain regions too with mirror neurons including the dorsal premotor cortex, superior parietal lobe, temporal gyrus, and cerebellum (21, 22).

Several important functions beyond the action domain have been theorized for the mirror neuron system (MNS). For example, it has been posited as a fundamental building block for understanding others' actions (23). It is suggested that the possible specific cognitive role of mirror neurons might be that of encoding the intentions of the actor (8, 24, 25). Also, the act of imitation has been suggested to rely on MNS (7, 26, 27). This idea seems eligible, considering that the parieto-frontal motor regions are known to be typically involved in the planning and execution of actions (21, 28-30). Iacoboni has suggested a ''core circuit'' for imitation that includes three regions, two of which include parts of MNS (31), although because monkeys are relatively poor in the task of imitation has brought arguments in this regard. Considering these findings there is an idea that the direct goal encoding feature of MNS provides a primary mechanism both for understanding other people and for imitating them (32). More recently, researchers suggest that MNS may play a role in human infants' ability to map similarities between self and others, and thus may be involved in providing a foundation for social–cognitive development (33). Additionally, there has been emphasis' on ties between MNS and empathy (34, 35), and MNS and language (36, 37).

To date, there has never been a systematic review of the studies which examine mirror mechanism in patients with schizophrenia. Based on a recent narrative review in Nature Reviews journal (38), findings in this regard are mixed and not compatible. This stresses the necessity of a systematic examination of the studies in this subject. In the current paper, we aim to review all the available literature regarding mirror mechanism examination in patients with schizophrenia and present an explicit summary of the available findings up to this date.

Objectives

To investigate the mirror mechanism in patients with schizophrenia and related disorders (psychosis spectrum disorder) and present an explicit view of available findings regarding this manner up to the date.

Methods

Design and methods used for this protocol review comply with Centre for Reviews and Dissemination (CRD's) Guidance For Undertaking Reviews in Healthcare (39), Meta-analyses of Observational Studies in Epidemiology (MOOSE) (40) and is reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) (1). Eligibility criteria were informed using the SPIDER (41) and MOOSE guidelines.

Eligibility criteria

(S) Sample: Adults of any age and sex with the diagnosis of schizophrenia, schizoaffective disorder, and psychosis spectrum disorder in general confirmed by a physician according to International Classification of Diseases (ICD) (6, 42, 43) or Diagnostic and Statistical Manual of Mental Disorders (DSM) (44, 45) guidelines, irrespective of the severity of disease and duration of illness. Participants with any other confirmed structural or functional neurologic disorders will be excluded.
(PI) Phenomenon of Interest: The mirror neuron system (MNS) functional integrity.
(D) Design: Observational cohort and cross-sectional studies.
(E) Evaluation: Electroencephalography (EEG), Magnetoencephalography (MEG), Transcranial magnetic stimulation (TMS), Functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), Eye tracking, and muscle activation (EMG).
(R) Research type: Qualitative, quantitative, and mixed-methods research could be searched for.

Information sources

The search will employ sensitive topic-based strategies designed for each database with no time frame limitations. There will be no language or geographical restrictions either. We will preform our search at 10th of February, 2021.
Databases:

- MEDLINE through PubMed
- Embase
- Science Citation Index – Expanded (Web of Science)
- Conference Proceedings Citation Index – Science (Web of Science)

Search strategy

Our search strategies for all the databases included in our study, namely MEDLINE (through PubMed), Embase, Science Citation Index – Expanded (Web of Science), and Conference Proceedings Citation Index – Science (Web of Science) are presented in appendix A.

Study records

Data management

Records will be managed through EndNote version X9 (46); specific software for managing bibliographies.

Selection process

Two reviewers (NH and AH) will independently screen the title and abstract of identified studies for inclusion. We will link publications from the same study to avoid including data from the same

study more than once. If any study cannot be clearly excluded based on its title and abstract, its full text will be reviewed. A study will be included when both reviewers independently assess it as satisfying the inclusion criteria from the full text. A third reviewer (AV) will act as arbitrator in the event of disagreement following discussion.

Data collection process

Using a standardized form, two reviewers (AR and MM) will extract the data independently. A third reviewer (AV) will independently check the data for consistency and clarity. We will attempt to extract data presented only in graphs and figures whenever possible but will include such data only if two reviewers independently obtain the same result. If studies are multi-center, then where possible we will extract data relevant to each. If necessary, we will attempt to contact study authors through an open-ended request to obtain missing information or for clarification.

Data items

Data extracted will include the following summary data: sample characteristics, sample size, type of modality used for examining MNS in participants, the task that was used for the study, founding sources, declarations of interests, results, and summary of the findings as either normal, abnormal, and mixed (indicating that different components of the data suggest different things, or that the reported results are not entirely statistically robust).

Outcomes and prioritization

Studies will be grouped according to the different modalities used, which may include Electroencephalography (EEG), Magnetoencephalography (MEG), Transcranial magnetic stimulation (TMS), Functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), Eye tracking, and muscle activation (EMG). However, studies using general behavioral measures (e.g. imitation tasks) and studies of reaction time during automatic imitation will be excluded. In the end, we will review other approaches that did not fit in the standard categorization of tasks, and also the findings from structural MRI studies.

Risk of bias in individual studies

Two authors (AR and MM) will independently evaluate the included studies for risks of bias. We will discuss any disagreement and document our decisions, and a third author (AV) will act as arbitrator in such a case. Cohen's κ will be used to assess agreement between reviewers. All tools and processes will be piloted before use. We will use the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (47). This tool consists of fourteen questions which will address the following: 1- Research question, 2 and 3- Study population, 4- Study eligibility criteria, 5- Sample size justification, 6- Whether the exposure assessed prior to outcome measurement, 7- Wether sufficient timeframe was given to see an effect, 8- Different levels of the exposure of interest, 9- Exposure measures and assessment, 10- Repeated exposure assessment, 11- Outcome measures, 12- Blinding of outcome assessors, 13- Followup rate, and 14- Statistical analysis. There are five possible answers to each question: yes, no, cannot determine, not applicable, and not reported. Finally, there are three possible judgments for the quality rating of each study: high quality, fair quality, and low quality. A high risk of bias translates to a rating of poor quality, while a low risk of bias translates to a rating of good quality. The tool, with the authors' judgment for a "yes" answer to each question, is presented in Appendix B.

Data synthesis

We will use R version 4 (48) as the software for our data synthesis. A meta-synthesis will be performed based on vote counting methods and results will be presented as a harvest plot. A summary of all studies included in the synthesis will also be presented. In this table we will present the following:

- Modality of the study (EEG, fMRI, etc.)
- Study ID
- Number of schizophrenia participants
- Mean age of participants (in years)
- Task: the task that was used with the modality.
- Results
- Summary: the results of each study will be summarized in terms of whether the paper provides evidence for an abnormal MNS in schizophrenia, a normal MNS, or evidence which is mixed. Mixed evidence can mean either that different components of the data suggest different things, or because the reported results are not entirely statistically robust.

Meta-bias

To evaluate the risk of reporting bias across studies, a test for funnel plot asymmetry will be conducted. This test examines whether the relationship between estimated effect size and study size is greater than chance (49). Funnel plots will be generated for visual inspection of potential publication bias. In the presence of publication bias, the plot will be symmetrical at the top, and data points will increasingly be missing from the middle to the bottom parts of the plot (50).

Confidence in cumulative evidence

The strength of the overall body of evidence will be assessed using the Confidence in Evidence from Reviews of Qualitative research method (CERQual) (51). This approach uses four components to evaluate confidence in the review findings. These include the methodological limitations of included studies, the relevance of the included studies to review questions, the coherence of the review findings, and the adequacy of the data that contributes to each review finding. In the first instance, MM will evaluate each finding using the four components of CERQual and a four-point scoring system ranging from 'no or very minor concerns' to 'substantial concerns'; AV then checks the evaluation. The review authors will meet and discuss the scores and assign each finding an overall CERQual assessment score. Each finding starts with a 'high confidence' score which could be downgraded to 'moderate confidence', 'low confidence', or 'very low confidence' if the CERQual process revealed concerns.

Appendices

Appendix A

Embase

#1. 'mirror neuron system':ab,ti
#2. 'mirror system':ab,ti
#3. 'motor resonance':ab,ti
#4. (neuron NEAR/5 mirror):ab,ti
#5. (brain NEAR/5 mirror):ab,ti
#6. 'mirror neuron'/exp
#7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8. 'schizophrenia spectrum disorder'/exp
#9. schizo*:ab,ti
#10. (psychosis NEAR/5 spectrum):ab,ti
#11. #8 OR #9 OR #10
#12. #7 AND #11
#13. #12 AND [embase]/lim

MEDLINE (through PubMed)

(mirror neuron system[tw] OR Mirror Neurons[mh] OR mirror neuron*[tw] OR mirror system[tw] OR motor resonance[tw]) AND (schizo*[tw] OR Schizophrenia[mh] OR psychosis [tw])

Web of Science

#1. TS=”mirror neuron system”
#2. TS=”mirror system”
#3. TS=”motor resonance”
#4. TS=(neuron NEAR/5 mirror)
#5. TS=(brain NEAR/5 mirror)
#6. #1 OR #2 OR #3 OR #4 OR #5
#7. TS=(schizo*)
#8. TS=(psychosis NEAR/5 spectrum)
#9. #7 OR #8
#10. #6 AND #9

Appendix B

NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (47)

Number	Question	Authors' judgment for "yes"
#1	Was the research question or objective in this paper clearly stated?	"Assessment of MNS in schizophrenia spectrum disorders patients" is clearly defined as an objective.
#2	Was the study population clearly specified and defined?	Baseline characteristics of the study population, specifically the definite diagnosis of schizophrenia spectrum disorders are stated.
#3	Was the participation rate of eligible persons at least 50%?	More than 50% of the eligible population participated in the study.
#4	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Inclusion and exclusion criteria were developed before recruitment or selection of the study population and the same underlying criteria were used for all of the subjects involved.
#5	Was a sample size justification, power description, or variance and effect estimates provided?	No: Most of our targeted studies will be explanatory in nature.
#6	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	In cohort studies, MNS evaluation was done after the diagnosis. In cross-sectional studies, the answer is "No".
#7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	In cohort studies, at least one year is passed after the diagnosis when MNS is evaluated. In cross-sectional studies, the answer is "No".
#8	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Not applicable: Our exposure (diagnosis of the disease) does not have variation in amount.
#9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Diagnosis of the disease was made by a trained physician based on the DSM or ICD criteria.
#10	Was the exposure(s) assessed more than once over time?	Not applicable: Multiple times of diagnosis of the disease I not necessary.
#11	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	It is clearly stated in the study that they evaluate MNS.
#12	Were the outcome assessors blinded to the exposure status of participants?	Assessors were blinded to the diagnosis of patients.
#13	Was loss to follow-up after baseline 20% or less?	In cohort studies, loss to follow-up was less than 20%. In cross-sectional the answer is "Not applicable".
#14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Regression methods were used for adjustment for baseline differences.

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