Review article

Lesion localization and performance on Theory of Mind tests in stroke survivors: a systematic review

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Abstract

Background: Theory of Mind (ToM) is the ability to attribute mental states to oneself and others. Individuals with a brain lesion following a stroke exhibit a compromised ability to perform ToM tasks. **Objective:** To analyze studies that evaluated ToM in stroke survivors considering the lesion localization and performance on ToM tests. **Methods:** The searches were carried out until November 28, 2018, using the following search terms: "social cognition" or "Theory of Mind" and "stroke". Searches were conducted in the PubMed, PsycInfo, Web of Science and Scopus data bases. The initial search led to the retrieval of 425 articles. After the exclusion of duplicates and the analysis of the titles, abstracts and full texts, 20 articles were selected for the present review. **Results:** The studies showed that patients with lesion in the right hemisphere present lower performance on ToM tasks compared to those with lesion in the left hemisphere. In addition, patients with lesion in the right hemisphere presented significant impairment in the performance on ToM tasks compared to healthy individuals. Furthermore, the studies that evaluated lesions in specific regions such as temporal lobe, prefrontal cortex, posterior parietal cortex, and temporo-parietal junction, indicated a significant deficit in ToM performance of these patients compared to healthy individuals. **Discussion:** This review showed that stroke survivors have a poor performance on ToM tasks. The right hemisphere and prefrontal cortex seem to be associated with the deficit of this ability.

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Keywords: Social cognition, Theory of Mind, stroke.

Introduction

The term "Theory of Mind" (ToM) emerged at the end of the 1970s with experimental studies on animal cognition. Premack and Woodruff[1] investigated the ability of chimpanzees to infer the intentions of humans in a problem situation shown on video. The results suggested that primates were able to understand and identify options compatible with these intentions.

Abilities related to ToM emerge throughout the development process[2]. ToM is the capacity to make inferences regarding the thoughts, intentions, beliefs and emotions of others to predict and explain their behavior[1]. The construct of ToM is comprised of affective and cognitive components[3]. The cognitive component regards the ability to distinguish the thoughts, beliefs and intentions of another person, whereas understanding the feelings or others is attributed to the affective component[4].

Neuroimaging studies report a network of active brain regions involved in the processing of ToM, including the anterior cingulate cortex, posterior cingulate cortex, medial prefrontal cortex, precuneus, inferior frontal gyrus, superior temporal sulcus and temporoparietal junction[2,5,6]. Therefore, brain lesions that affect these regions may result in an impaired ability of ToM.

Studies on stroke survivors commonly investigate the influence of the cerebral lateralization in the ability of ToM. Evidence indicates that individuals with the right hemisphere affected have a deficit regarding the ability of ToM compared to patients with lesion in the left hemisphere[3]. According to Tompkins *et al.*[7] right hemisphere brain lesions can result in impaired communication and social interactions. However, divergent results are found on the lateralization of the function of ToM, indicating that stroke patients, regardless of the location of the lesion, have significant impairment in the ability of ToM compared to the control group[8].

The aim of the present study was to perform a systematic review of all studies published that have evaluated ToM in stroke survivors considering the lesion localization and performance on ToM tests.

Methods

A systematic review was performed of studies conducted to evaluate ToM in adult stroke survivors. The searches were carried out until November 28, 2018 in the databases: Pubmed, PsycInfo, Web of Science and Scopus, using the following search terms: ("social cognition" or "Theory of Mind") and stroke. The inclusion criteria were studies published in English that evaluated post-stroke ToM in individuals aged 18 years or older. No restriction was imposed on the year of publication. Studies that evaluated ToM in specific clinical samples (individuals with dementia, schizophrenia, autism, Williams syndrome, Parkinson's disease, epilepsy, etc.) in the absence of stroke and post-stroke neuroimaging studies that did not evaluate ToM were excluded from the review. Books, book chapters, opinions, case studies, bibliographic/systematic reviews and meta-analyses were also excluded.

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Two independent researchers performed the data extraction and documented the authors' names, year of publication, sample size, sex, age and schooling of the participants, time elapsed since the stroke event, site of the brain lesion and instruments used to assess ToM. Divergences of opinion between the reviewers were discussed until a consensus was reached. The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[9].

The initial search led to the retrieval of 425 articles. After the removal of duplicates, the titles and abstracts of 268 articles were analyzed for eligibility, 172 of which were preselected. Following the full-text analysis, 152 articles were excluded and 20 were selected for the present review. Figure 1 displays the flowchart of the selection process.

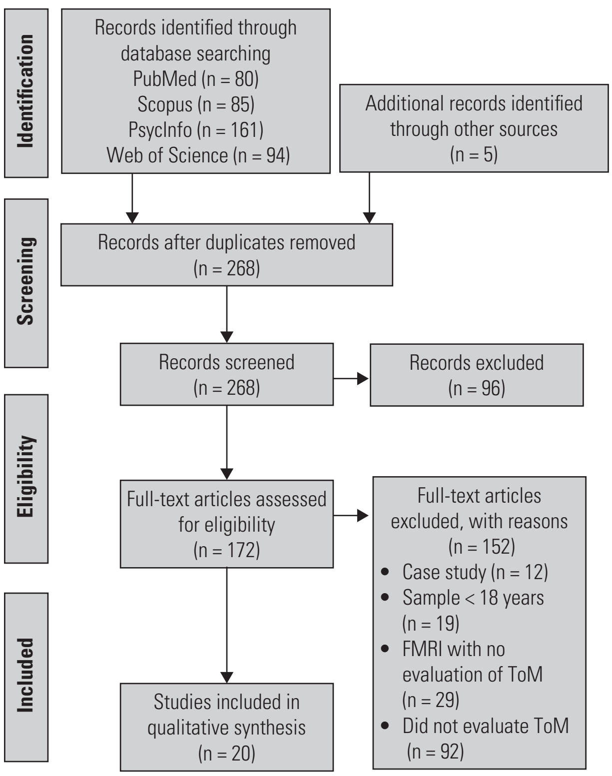

Figure 1.

In addition, the studies selected in the present review were evaluated for methodological quality based on the guidelines of strengthening the reporting of observational studies in epidemiology (STROBE). This instrument consists of 22 check items and aims to provide greater transparency and improve the quality of the description and presentation of observational study findings[10]. We also used as a basis the Dictionary of STROBE, indicated by the authors as an important theoretical framework for the critical analysis of scientific articles[11].

Regarding the score, studies with a score of 80 to 100% are considered studies that have a strong methodological quality. Studies with a score of 60%-79% are classified as moderate methodological quality, and studies with lower than 60% scores are classified in the *STROBE checklist*[12].

Results

Table 1 displays the data extracted from the 20 articles selected for the present review. The articles were published between 1996[13] and 2017[4]. The sample size ranged from 11[14] to 80[4] participants, the majority of whom was male (55.9%), and mean age ranged from 34.12[15] to 73 years[16,17]. Educational level of the participants ranged from 7.3[18] to 15 years of study[19]; five articles did not specify the schooling of the participants[20-24].

Regarding the affected region of the brain, six studies evaluated patients with damage to both hemispheres[3,4,8,13,17,18]. Three studies showed that patients with lesion in right hemisphere present significant impairment in the performance on ToM tasks compared to patients with lesion in the left hemisphere[3,13,17] and control group[17]. In contrast, Yeh and Tsai[8] and Pluta *et al.*[4] demonstrated that patients with stroke showed impairment in the ToM abilities compared to control group, regardless of the hemisphere of the lesion. The study of Surian and Siegal[18] found no association between the performance on ToM tasks and post-stoke lesion.

In addition, seven studies evaluated patients with damage only in the right hemisphere[7,16,19,21,22,25,26] and only one study did not show impairment in the ToM abilities in patients with lesion in the right hemisphere compared to healthy patients[7].

Seven studies evaluated specific regions of the brain, such as the temporal lobe, prefrontal cortex, posterior parietal cortex and temporoparietal junction[15,20,23,24,27,28], and these patients showed significant impairment on the performance on ToM tasks compared to healthy individuals. Roca *et al.*[14] did not specify the site of the lesion. The time elapsed since the stroke event ranged from three weeks[24] to 23 years[17]. Four studies did not specify the time elapsed since the stroke event[6,14,19,23].

For the evaluation of ToM, the most frequently used tasks were: The False Belief and True Belief task[4,7,13,15-20,23,25-27], which is composed of stories that require the attribution of false and true beliefs, with the aim of verifying the participant's ability to make inferences about mental states, and these can be divided into false first-order beliefs, which concerns understanding the mental state of the other and second order, which is ability to understand what someone thinks about what someone else thinks; The FauxPas Detection test[8,14,15,28] examine the individual's ability to understand an embarrassing social situation, such as when one individual says something to another without considering that he would not like to hear[15]; The Reading the Mind in the Eyes test[3,24,28], which consists of presenting black and white photographs of the eye region, in which participants should choose a word that best describes what the person in the image is thinking or feeling, with the intention of assess the ability to interpret the mental states of the other.

In relation to the methodological quality of the studies, of the 20 studies evaluated according to STROBE, six studies[14,19,20,23,27,28] obtained scores lower than 60% and were considered with poor methodological quality and fourteen[3,4,7,8,13,15-18,21,22,24-26] studies obtained a score of 60% to 79% and were classified with moderate quality. None of the studies evaluated reached a score above 80% and therefore no study was considered with strong methodological quality. The main weaknesses identified according to STROBE were: non-identification of the study's design in the title or abstract (n = 20), absence of flow diagram (n = 19), absence of explanation of how the study size was arrived at (n = 7), absence of explain how missing data were addressed (n = 19) and the description of sensitivity analyses (n = 17).

Discussion

The studies included in the present review generally indicate that stroke survivors have a poorer performance on ToM tasks. Moreover, the association between a lesion in the right hemisphere and the performance on these tasks was a predominant characteristic of this review.

In general, patients with lesion in the right hemisphere showed lower performance on ToM tasks compared to those with lesion in the left hemisphere. Furthermore, when compared to healthy individuals, patients with lesion on the right hemisphere present impairment on the performance on ToM tasks. Likewise, patients with lesions in specific regions, such as temporal lobe, prefrontal cortex, posterior parietal cortex and temporoparietal junction, presented deficit in the performance on ToM tasks in relation to the healthy individuals.

Table 1. Characteristics of the selected studies according to inclusion criteria

Authors/Year	Sample	Sex (M:F)	Age	Education (years)	Lesion site	Time post stroke	ToM assessment tool	Main findings
Apperly *et al.*, 2004[20]	12	SP: 10:2	SP: 55.2 (±13.5)	-	Frontal Parietal temporal lobes.	8 (±4.2) years	False Belief Tasks	Lesions in the temporoparietal region impair the ability to perform the False Beliefs task.
Besharati *et al.*, 2016[16]	45	AHP: 6:9 HP: 8:7 HC: 9:7	AHP: 73.00 (±22.0) HP: 68.00 (±27.0) HC: 71.00 (±7.0)	AHP: 12.00 (± 3.0) HP: 12.00 (±3.0) HC: 13.00 (±6.0)	Right hemisphere	-	Adapted Stories inference of beliefs, intentions and emotions	Anosognosia group performed worse than both control groups when having to perform tasks from a third versus a first person perspective.
Champagne-Lavau *et al.*, 2009[26]	30	RHL: 6:9 HC: 7:8	RHL: 60.9 (±11.7) HC: 60.7 (±12.8)	RHL: 11.7 (±3.1) HC: 11.7(±3.2)	Right hemisphere	1-4 months	False belief task	Patients with right frontal and internal capsule lesions presented pragmatic and ToM deficits compared to HC group.
Griffin *et al.*, 2006[19]	31	RHL: 6:5 HC: 7:13	RHL: 61.0 HC: 66.0	RHL:14.0 HC: 15.0	Right hemisphere	-	A graded (first order, second order) ToM task with non-mentalistic control questions	RHL patients differed from non-brain-damaged controls in the ability to attribute second order intentional states.
Hamilton *et al.*, 2017[3]	70	RHL: 7:8 LHL: 7:8 HC: 18:22	RHL: 67.80 (±14.1) LHL: 67.73 (±9.9) HC: 66.63 (±12.7)	RHL: 11.73 (±3.0) LHL:10.87 (±2.2) HC: 12.13(± 3.5)	Left hemisphere and Right hemisphere	RHL: 71.0 (±32.4) days LHL: 77.47 (±32.4) days	RMET and Eyes control task	The results showed that stroke participants with RHL were significantly more impaired on the visual RMET than those with LHL, who performed similarly to healthy controls.
Happé *et al.*, 1999[17]	38	RHL: 5:9 LHL: 4:1 HC: 9:10	RHL: 64 LHL: 67 HC: 73	RHL: 13.4 LHL: 12.6 HC: 14.6	Right hemisphere and Left hemisphere	RHL: 4 months to 23 years LHL: 12 months to 21 years	ToM stories and non- mental stories.	RHL patients showed evidence of ToM impairment compared to LHL patients and healthy controls.
Humphreys and Bedford, 2011[23]	24	PPC/TP: 4:2FL: 6:0 LC: 6:0 HC: 4:2	PPC/TPJ: 68.33(±6.3) FL: 63.5 (±14.2) LC: 56.16 (±14.2) HC: 67.5	-	Posterior parietal cortex and Temporoparietal junction	-	Social Simon	Patients with brain injuries present impairment on ToM tasks related to the capacity to respond to social stimuli.
Mah *et al.*, 2004[27]	64	SP: 30:3 HC: 23:8	SP: 52.5 (±7.5) HC: 54.5 (±9.8)	SP: 14.1 (±2.5) HC: 14.9 (±2.0)	Prefrontal cortex	-	Interpersonal Perception Task	All patients showed poorer insight into their deficits, relative to healthy volunteers.
Martin and Mcdonald, 2006[21]	42	RHL: 13:8 HC: 6:15	RHL: 69.2 (±14.8) HC: 68.5 (±14.7)	-	Right hemisphere	5.7 months	Test of ToM and Pragmatic Ability	Patients with RHL demonstrated significant difficulty on tasks that used the social context to interpret pragmatic inferences.
Pluta *et al.*, 2017[4]	80	RHL: 15:14 LHL: 12:12 BL: 5:0 HC: 9:13	RHL: 57.7 (±13) LHL: 60.2 (±10) BL: 45.5 (±19.8) HC: 55.4 (±10)	RHL: <12: 18/ >12: 9 LHL: <12: 10 / >12: 14 BL: <12: 3 / >12: 2 HC: <12: 12 / >12: 10	Left hemisphere, right hemisphere and bilateral	RHL: 24.8 (±35.4) months LHL: 28.4 (±28.1) months BL: 13 (±15.5) months	18 short vignettes (false beliefs, sarcasm, white lie)	The results showed that there were no differences between RHD, LHD, and BD patients in any of the ToM tasks. Patient group demonstrated impaired performance on all ToM tasks compared to a control group.
Roca *et al.*, 2013[14]	11	9:2	50.6 (±12.1)	12.5 (±2.9)	-	-	The Faux Pas task	Patients with cerebellar strokes did not show impairment on the test.

Authors/Year	Sample	Sex (M:F)	Age	Education (years)	Lesion site	Time post stroke	ToM assessment tool	Main findings
Shamay-Tsoory *et al.*, 2005[15]	52	FL: 20:6 PL: 8:5 HC: 10:3	FL: 34.12 (±14.0) PL: 40.46 (±5.38) HC: 34.12 (±12.59)	FL: 12.46 (±1.9) PL: 12.9 (±2.1) HC: 14.4 (±3.4)	Prefrontal cortex and posterior lesions	6 months, except one patient who was assessed 3 months after trauma	false belief task, detection of irony and identifying social faux pas	Lesions in the right ventromedial area were associated with more severe ToM deficit compared with patients with posterior lesions and normal control subjects.
Siegal *et al.*, 1996[13]	28	RHL: 7:10 LHL: 8:3	RHL: 69.2 (±10.9) LHL: 70.3 (±9.7)	RHL: 8.6 LHL: 8.2	Right hemisphere and Left hemisphere	RHL: 1-24 months LHL: 1-68 months	False belief and True Belief task	Patients with RHL have difficulties understanding the false beliefs tasks.
Surian and Siegal, 2001[18]	64	RHL: 9:7 LHL: 8:8 HC: 13:19	RHL: 62.3 (±12.3) LHL: 62.8 (±15.5) HC: 64.5	RHL: 7.3 (±3.1) LHL: 7.6 (±2.5) HC: 7.3	Right hemisphere and Left hemisphere	RHL: 9.9 months (±13.7) LHL: 8.6 months (±8.1)	False Belief and True Belief stories.	The performances on the ToM tasks of the RHL and LHL groups did not differ significantly from controls
Tompkins *et al.*, 2008[7]	60	RHL: 3:9 HC: 9:19	RHL: 64.4 HC: 60.4	RHL: 14.6 (±3.2) HC: 13.9 (±2.2)	Right hemisphere	65.7 (±52.2) months	Narrative stimuli that targeted either a mental or a non-mental causal inference.	The group with RHL did not show impairment on the test.
Weed *et al.*, 2010[22]	21	RHL: 8:3 HC: 4:6	RHL: 65.0 HC: 65.0	-	Right hemisphere	3.09 (±1.7) months	Animated films with moving geometric shapes	RHL group displayed impaired ability to discriminate between film categories and exhibited bias when attributing mental states to others.
Wilkos *et al.*, 2015[24]	19	SP: 5:3 HC: 6:5	SP: 63.7 (±7.9) HC: 49.6 (±12.2)	-	Unilateral Thalamic	3 weeks	RMET	Compared to healthy controls, patients showed significantly worse performance on RMET task.
Winner *et al.*, 1998[25]	33	RHL: 6:7 HC: 14:6	RHL: 59.5 (±12.2) HC: 66.5 (±8.2)	RHL: 14.5 (±2.6) HC: 14.2 (±2.4)	Right hemisphere	5.6 (±5.2) years	Sixteen short lie or joke stories	RHL patients performed significantly worse than control subjects on one of two measures of second-order belief.
Xi *et al.*, 2013[28]	39	TLCI: 16:3 HC: 13:7	TLCI: 55.16 (±14.0) HC: 56 (±6.7)	SP: 10.11 (±3.3) HC: 10.95 (± 2.3)	Temporal lobe	36.42 days (±8.9)	Recognition of faux pas and RMET tasks	TLCI group performed significantly worse on tasks compared to HC group.
Yeh *et al.*, 2014[8]	74	LHL: 8:6 RHL: 9:11 HC: 22:18	LHL: 57.79 (±10.8) RHL: 63.85 (±11.5) HC: 60.20 (±11.87)	LHL: 9.64 (±3.5) RHL: 8.70 (±4.6) HC: 9.10 (±3.5)	Left hemisphere and Right hemisphere	LHL: 18.18 (±6.5) months RHL: 20.45 (±7.9) months	The Faux Pas task	Patients with stroke were significantly impaired in both cognitive and affective ToM compared to a control group.

M: male; F: female; HC: healthy control; SP: stroke participants; RHL: right hemisphere lesion; LHL: left hemisphere lesion; BL: bilateral lesions; FL: frontal lesions; LC: lesioned controls; PPC: posterior parietal cortex; TPJ: temporoparietal junction; PL: posterior lesion; AHP: anosognosia for hemiplegia; HP: hemiplegic group; RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; TLCI: temporal lobe cerebral infarction.

Studies that evaluated the cerebral location of the stroke event found heterogeneous results regarding the lateralization of the function of ToM. Stroke survivors with the right hemisphere affected exhibited greater impairment on tasks that evaluate ToM than those with lesions in the left hemisphere[3,13,17] or healthy individuals[19,21,22,25]. In contrast, Pluta *et al.*[4] compared the performance on ToM tasks among individuals with right hemisphere lesions, left hemisphere lesions and bilateral lesions and found that stroke survivors exhibit impairment on these tasks, but found no difference with regard to the site of the lesion. Likewise, Surian and Siegal[14] found no significant difference in the performance on the False Belief and True Belief test between two groups separated into right hemisphere and left hemisphere lesions.

Tompkins *et al.*[7] also found no difference on ToM tasks between patients with a right hemisphere lesion and a control group. Happé *et al.*[17] found that eight out of 14 patients in the group with right hemisphere lesions had a poorer performance on ToM tasks, whereas only two out of 21 patients with left hemisphere lesions exhibited a compromised ability on these tasks in the study by Tompkins *et al.*[7], indicating greater impairment on ToM tasks following a stroke in the right hemisphere. However, it is important to stress the methodological difference between the studies, as different tests were used to assess ToM[7]. According to Happé *et al.*[17] the association between right hemisphere lesions and performance on ToM tasks may stem from the characteristics of the lesion; stroke survivors with the right hemisphere affected may have more or more severe lesions in comparison to those with the left hemisphere affected.

In the study by Roca *et al.*[14] patients with cerebellar strokes demonstrated no impairment on the Faux Pas Detection task. According to the authors, these tasks require other functions that may be related to the cerebellum, such as language, which may have exerted an influence on the results.

In a study comparing abilities on pragmatic ToM tasks and executive functions in stroke survivors with right hemisphere lesions and healthy individuals, Champagne-Lavau *et al.*[26] found that the ability to understand pragmatic aspects of language is closely associated with the ability to make inferences regarding the intentions of others. The researchers also found an association between an impaired ToM and executive dysfunction in subgroups of individuals with damage in the right hemisphere.

Shamay-Tsoory *et al.*[15] evaluated patients with lesions in the prefrontal cortex, posterior lesions and participants without lesions and found that those with prefrontal lesions, specifically ventromedial prefrontal lesions, exhibited impairment on ToM tasks. Likewise, Mah *et al.*[27] compared patients with lesions in the prefrontal cortex to healthy volunteers and found that the patients with lesions, especially in the dorsolateral prefrontal cortex, demonstrated impaired abilities regarding ToM. These findings support that notion that the prefrontal cortex is associated with ToM skills and that the ventromedial prefrontal cortex is essential to the regulation of emotions[29].

According to Shamay-Tsoory *et al.*[15], the difference between sites and the asymmetry of the lesions may influence the results of ToM tasks due to the involvement of different cognitive processes. Stroke is associated with greater impairment in social cognition assessments that require other cognitive processes, such as working memory, language, executive function and attention, and which may also be affected post-stroke[3]. In addition, it is expected that the impairment after stroke is greater for more complex second-order tasks compared to the first order tasks of the ToM and for the classification of emotions[26]. Therefore, the choice of the task and lesion site may influence the results of the studies.

It is known that patients with lesion in the right hemisphere seem to perform worse in the ability to attribute intentional second-order states compared to first-order mental states[19,25]. There is also evidence that these tasks may not allow the distinction of effects in patients with stroke and healthy controls[7]. For example, in the study by Griffin *et al.*[19], RHL patients differed from non-brain-damaged controls in the ability to attribute second order intentional states, however, these authors were not found differences between groups with regard to attribute first order intentional states.

Another question considered as an influencing factor that can influence in the performance in the of ToM tasks is the tool used. Evidence indicates that this task RMET can have biased responses and, consequently, limit its psychometric validity[30]. The study by Hamilton *et al.*[3] used the RMET task to assess the difference between the performance of in ToM in of patients with RHL, LHL and healthy controls, and the results showed that stroke participants with RHL were significantly more impaired on the RMET than those with LHL, who performed similarly to healthy controls. The authors present as a limitation the use of RMET only for the assessment of ToM, since the test involves the recognition of complex emotions and, therefore, evaluates this ability restrictively.

Concerning to evaluation, the articles included in this review used a wide variety of tools to evaluate ToM. In overall, the studies found indicate that ToM evaluation has as purposes: (i) detect mistakes and contextual information using, for instance, false beliefs tasks[4,7,13,15-20,23,25-27] e The Faux Pas Detection test[8,14,15,28]; (ii) analyze the pragmatic understanding discourse[21]; (iii) verify the non-verbal contents abstraction through The Reading the Mind in the Eyes test[3,24,28] and tasks composed of geometric elements[22]; in addition to studies that integrate these different evaluation methods[15,28]. The variability of measures of ToM assessment used by the selected studies may be considered as limitation, as it made difficult the systematization and the comparison between the results, invalidating the meta-analysis accomplishment.

With regard to the time post stroke event, none of the articles selected for the present review discussed the influence of this variable on the results. Therefore, further studies are needed to investigate this aspect. Another topic that could be explored by new studies is the frequency of people post stroke with significant damage on ToM ability.

The limitation of the present review resides in the inconsistency of some of the data extracted for the construction of the table in the results section, as some information considered pertinent for a systematic evaluation of this topic was missing. Furthermore, the absence of realization of cross-reference search, based on the descriptors used, may have made it difficult to refinement the articles, limiting the findings found. Finally, the general low quality of the articles analyzed can also be considered as a limitation.

This review has important clinical implications, since an impaired ability of ToM can affect the process of capturing and transmitting information through social interaction. Therefore, accurate identification of impaired ToM ability based on clinical evaluation is essential to indicate the most appropriate treatment.

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