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Toward social neuropsychology of epilepsy: a meta-analysis on social cognition in epilepsy phenotypes and a critical narrative review on assessment methods

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Abstract

Background: The aim of this review is to (a) characterize social cognition impairments in the domains of emotion recognition (ER) and theory of mind (ToM) in patients with epilepsy and (b) to review assessment tools with a focus on their validity and usability in clinical practice.

Methods: An electronic search for clinical studies investigating social cognition in epilepsy populations vs healthy control subjects (HC) yielded 53 studies for the meta-analysis and descriptive review.

Results: Results suggest that (1) social cognition is significantly impaired in patients with temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE) and patients with epilepsy not originating within the temporal or frontal lobes including idiopathic generalized epilepsies (eTLE/eFLE); (2) there is no significant difference between eTLE/eFLE and TLE regarding ER, while TLE and FLE patients perform worse than those with eTLE/eFLE, without significant differences between FLE and TLE regarding ToM ability. A descriptive analysis of the most commonly used assessment tools and stimulus material in this field revealed a lack of ecological validity, usability, and economic viability for everyday clinical practice.

Conclusions: Our meta-analysis shows that patients with epilepsy are at a significantly increased risk of deficits in social cognition. However, the underlying multifactorial mechanisms remain unclear. Future research should therefore specifically address the impairment of processing and methodological problems of testing.

Keywords: Social cognition, Epilepsy, Temporal lobe epilepsy, Frontal lobe epilepsy, Emotion recognition, Theory of mind

Background

Social behaviour and social cognition shape the nature of human behaviour [1] and remain essential throughout the entire lifespan [2]. A majority of daily activities are guided by socio-emotional motivations and needs. Consequently, impairment in socio-cognitive abilities

is associated with reduced psychosocial well-beings in clinical populations [3, 4]. Furthermore, socio-cognitive impairment seems to be a serious phenotype in many psychiatric, developmental, and neurological disorders, including epilepsy [5]. It is a great step forward that the most recent version of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) from the American Psychiatric Association [6] highlights the clinical importance of social cognition by recognizing it as a core neurocognitive domain.

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Social cognition can be defined as the ability to construe representations about the intentions and motives of others, their mental states, the relationships between oneself and others, as well as the ability to apply those representations to govern social behaviors [7, 8]. In clinical research, social cognition is often divided into the domains of empathy, theory of mind (ToM), and emotion recognition (ER). Most often, it is assessed through neuropsychological performance tests for ER and ToM. The former is usually assessed through the inference of basic emotions based on socio-emotionally salient, context-free, non-verbal sensory input, such as facial expressions, prosody and gait, while the latter implies the inference of more complex mental states, such as motivations, intentions, thoughts, desires, plans, beliefs, and complex emotions (e.g. [7, 9–17]). Social cognition enables us to be engaged in social activities and relationships to satisfy our social needs [18], and accumulate individual social capital (i.e., social integration, social support, social network size, etc.), which constitutes a key factor in subjective well-being and health [19–23]. Epidemiological studies have revealed that the major social determinants of quality of life (QoL) are at a considerable risk of impairment in patients with epilepsy [24, 25].

Correct interpretation of social signals and behaviour is a prerequisite for successful interpersonal interaction [26–28]. Difficulties in social competence in patients with epilepsy may arise from a number of interrelated factors. From the perspective of social, clinical and developmental psychology, interacting disease-related social and intrapsychic factors can impact on social skills and engagement [29]. From the traditional neuropsychological perspective of the twentieth century, social difficulties may result from cognitive impairment, such as impaired speed and capacity of information processing, attention deficits and memory impairments, which are common in this population [29]. The psychiatric perspective concerns higher prevalence of affective disorders in patients with epilepsy than in the general population [30] and higher rate of fatigue and attention deficit hyperactivity disorder [31]. These alterations may have an impact on social engagement and functioning and result in an impaired coping ability and a poor perceived QoL [24]. A complementary perspective comes from neuroscience and the relatively new area of social cognition. In this discipline, social cognition is defined as a form of information processing that contributes to the correct perception of dispositions and intentions of others [32] and encompasses a wide range of sub-processes. Effective social cognition relies on the exchange of signals, which can be processed at an automatic and controlled level and influenced by motivational aspects [33]. These processes act rapidly in different sensory modalities in parallel, provide social

information from others and draw on implicit as well as explicit memories [33, 34]. Imaging and lesion studies have revealed that the cerebral networks employed in social cognition [11, 35–39] are those frequently affected in patients with temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) [27, 40–47].

To date, five meta-analytic reviews have been published since 2015 regarding social cognition in patients with epilepsy [48–52]. The findings of Stewart et al. [48] revealed ToM deficits in adults with TLE and FLE, but not in adults with focal seizures outside temporal and frontal structures (extra-temporal, extra-frontal lobe epilepsy; eTLE/eFLE), while ToM deficits were also observed in children with generalised seizures (caveat: only two studies with adult patients with seizures outside temporal and frontal structures and two studies with children with generalised seizures were included). Edwards et al. [49] found large deficits regarding ER in patients with epilepsy, with TLE patients being significantly impaired on all emotion types except surprise, and patients with genetic generalised epilepsy being significantly impaired in anger, disgust and fear recognition. They also found that in patients with TLE, younger age was associated with lower accuracy. Monti and Meletti [50] reported that ER deficits are consistently observed across studies in patients with TLE, with impaired visual and fear recognition being the most consistently reported deficit, followed by deficits in sadness and disgust recognition, and conflicting evidence regarding the severity of ER deficits in right and left TLE. Furthermore, Bora and Meletti [51] found significant deficits in ToM and facial ER in patients with TLE. They found no significant difference in social cognition between TLE patients with and without medial temporal lobectomy, while earlier onset of seizures was associated with ToM impairment and right-sided TLE was associated with more severe deficits in recognition of fear, sadness and disgust. The most recent meta-analysis [52] reported that FLE and TLE patients have difficulties in all aspects of social cognition relative to the non-clinical controls, while the effect sizes were larger for ToM relative to ER, and the right TLE patients performed significantly worse than the left TLE patients, specifically in the ToM domain.

As Henry et al. [1] pointed out, although the DSM-5 [6] formally recognizes social cognition as a core neurocognitive domain, it does not name or recommend any specific tests for clinical practice. Despite the growing amount of research on social cognition in epilepsy patients and other clinical populations, there is still a paucity of viable and standardized assessment tools for neuropsychological clinical practice with valid norms, satisfactory psychometric properties [1] and usability, especially for non-English speaking populations,

although some attempts have been made in recent years [53, 54]. Two main critiques of existing assessment tools are their low ecological validity / artificiality [50, 54, 55] and their narrow scope regarding specific subfunctions [53]. The latter also affects the usability and economic viability of these tests, since global testing *via* the use of multiple tests for narrowly defined subfunctions in order to broadly assess social cognition becomes too time-consuming for standard clinical practice [53]. For an overview regarding the most commonly used assessment tools for social cognition in epilepsy research, see Ziaei et al. [52].

In this meta-analytic review, we set out to explore the social functioning of patients with FLE, TLE and eTLE/eFLE and to analyse the predominant assessment tools for social cognition in patients with epilepsy, in particular with regard to their viability for everyday clinical practice and ecological validity.

Methods

This meta-analytic review follows the PRISMA recommendations as closely as feasible [56, 57].

Search strategy

An electronic search strategy was used to identify published studies investigating the relationship between social cognition and epilepsy. Original research articles were identified and retrieved *via* EBSCO (APA PsycInfo and APA PsycArticles) and Embase (Medline and Embase). No date limits were placed on any of the database searches. The following search string was used (title search):

((affect* OR emot* OR expression* OR social*) AND (perce* OR identif* OR recog* OR process*)) AND (epilepsy OR epilep* OR seizure* OR ictal* OR convulsion*) NOT (mice OR mouse OR rat* OR rodent*) OR ((tom OR ttom OR (theory AND of AND mind) OR mentalizing OR mentalising OR empath* OR mindreading OR (mind AND reading) OR (social AND inference) OR (pragmatic AND ability) OR pragmati* OR (social AND predictive AND coding) OR (interpersonal AND predictive AND coding) OR (social AND perception)) AND (epilepsy OR epilep* OR seizure* OR ictal* OR convulsion*) NOT (mice OR mouse OR rat* OR rodent*)) OR ((social AND cognition) AND (epilepsy OR epilep* OR seizure* OR ictal* OR convulsion*) NOT (mice OR mouse OR rat* OR rodent*)).

Relevant reviews were consulted to refine the literature search by combining and slightly adjusting their search strings (title and abstract search) to detect subsequent articles [48–52]:

((face OR facial) AND (affect* OR emotion* OR expression*) AND (perce* OR identif* OR recogni* OR process*)) AND ((epilepsy OR epilep* OR seizure* OR (epileptic AND seizure) OR convulsion)) OR ((TLE AND emotion recognition) OR (Temporal lobe epilepsy AND emotion recognition) OR (Amygdala AND emotion recognition) NOT (mouse OR rat OR mice)) OR (((Theory of Mind) OR (Theory AND of AND mind) OR (social cognition) OR (social AND cognition) OR (social perception) OR (social AND perception) OR (social behaviour) OR (social AND behaviour) OR (perspective taking) OR (perspective AND taking) OR (mentalising) OR (mentalizing) OR (mind reading) OR (mind AND reading) OR (empathy)) AND ((epileps*) OR (seizure*))).

Backward searching (screening the reference lists of retrieved articles and reviews) and forward searching (subsequent articles citing the retrieved relevant articles) were performed in relevant articles (primary studies and reviews).

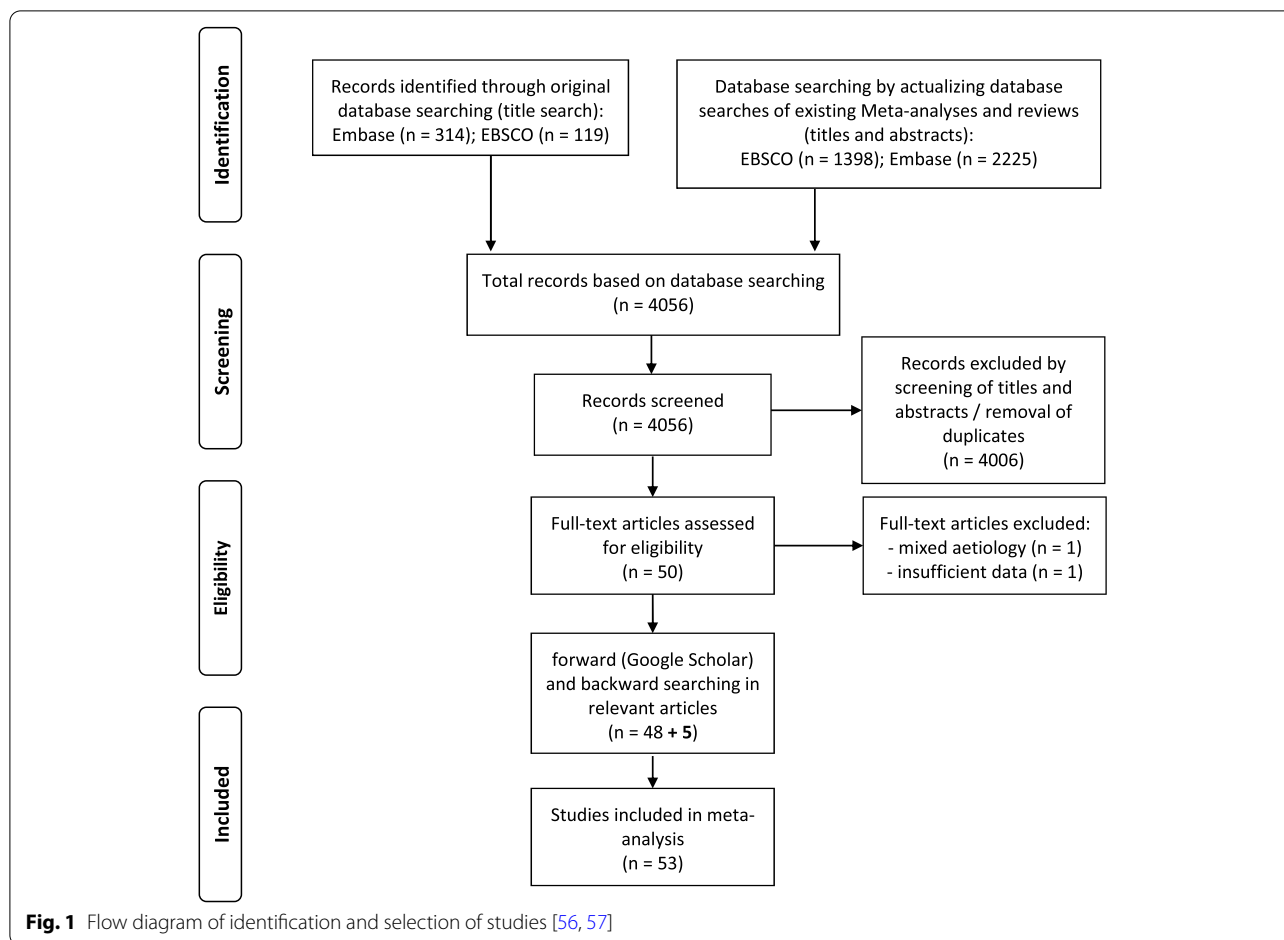
The search for relevant articles was finished on June 20th 2021.

Study selection

The titles and abstracts of articles retrieved in the identification process were screened to exclude irrelevant articles. For the included records after the initial screening process, the full articles were inspected to determine the eligibility. The identified studies were included for further statistical and descriptive analysis if they met the following criteria: the diagnosis of an epileptic disorder, the patients were aged 18 and above (mean rounded up, or range 18 and above on the lower end); and behavioral data relating to a social cognitive task in one or more of the following domains were reported; emotion recognition and/or theory of mind. Furthermore, studies needed a control group with no neurological or psychiatric disorders; every study required at least ten participants in the control group and epilepsy group each. If sufficient data were available, pooled effect sizes were calculated and information on sample characteristics and paradigms was extracted from each study. If the data were insufficient for effect size calculation, the authors were contacted. If the authors did not respond after 8 weeks, effect sizes were extracted from previously published meta-analyses [48–52], if available.

Literature search results

After the process of identification, screening and eligibility assessment, the literature search yielded a total of 53 studies that were ultimately included in the meta-analysis and descriptive review (for details, see the PRISMA flow-chart in Fig. 1).



Regarding ER, 31 studies [41, 54, 58–86] were included in the TLE subgroup for inferential statistical analysis with a total of 1235 TLE patients and 908 healthy control subjects (HCs), while only 4 studies [18, 87–89] were included in the eTLE/eFLE subgroup with a total of 85 eTLE/eFLE patients and 122 HCs. Only one study [90] reported a comparison between FLE patients and HCs, which was therefore not included in the subgroup analysis.

Regarding ToM, 15 studies [54, 58, 60, 63, 74, 91–100] were included in the TLE subgroup with a total of 617 TLE patients and 449 HCs. The FLE subgroup consisted of 5 studies [42, 90, 101–103] with a total of 145 FLE patients and 182 HCs, the eTLE/eFLE subgroup of 6 studies [18, 43, 87, 88, 104, 105] with a total of 157 eTLE/eFLE patients and 212 HCs.

For further details regarding sample characteristics, see Table 1 for TLE, Table 2 for FLE, and Table 3 for eTLE/eFLE.

Analysis

Effect sizes were calculated for results of tests of ER and ToM separately. If more than one effect size was extracted per study and function (ER/ToM), the mean effect size was calculated for further inferential statistical analysis, including subgroup analyses between TLE, FLE and eTLE/eFLE. If two or more of those subgroups were reported in a single study, the study was assigned to the subgroup with the smaller overall number of studies included only to avoid partial statistical dependency/redundancy due to overlapping control groups across studies. In these cases, we summarized those studies with between-group comparisons of different types of epilepsy patients separately. We used *Meta-Essentials* [106, 107] (a set of Excel workbooks) for the meta-analyses including the subgroup-analyses.

For a descriptive review regarding ER and ToM paradigms, pooled effect sizes (*hedges' g = d*), the numbers of studies and subjects for each paradigm were calculated individually.

Table 1 Sample characteristics of studies comparing TLE patients *versus* HC

References	Sample characteristics Group size [mean age \pm SD; Male:Female]	Social cognition: subfunction
Ahs et al., 2014 [82]	IMTLE = 9 [44.8 \pm 12.5; 2:7] rMTLE = 8 [47.7 \pm 9.4; 4:4] HC = 19 [46.1 \pm 14; 9:10]	ER
Amlerova et al., 2014 [58]	lpreTL = 24 [33 \pm 10; 12:12] lpostTL = 13 [33 \pm 7; 6:7] rpreTL = 22 [41 \pm 11; 14:8] rpostTL = 15 [35 \pm 8; 13:2] HC = 20 [33 \pm 13; 6:14]	ER, ToM
Anderson et al., 2000 [83]	ITL = 11 [32 \pm 8; 3:8] rTL = 12 [38 \pm 8; 4:8] HC = 23 [38 \pm 8; 7:16]	ER
Arani et al., 2020 [84]	TLE = 60 [n.a. \pm n.a.; n.a.] (age range: 20–50 years) HC = 60 [n.a. \pm n.a.; n.a.]	ER
Bala et al., 2018 [91]	ATL = 19 [35.94 \pm 6.85; 10:9] MTLE = 21 [33.09 \pm 11.41; 9:12] HC = 20 [30.23 \pm 11.49; 10:10]	ToM
Batut et al., 2006 [85]	IMTLE = 6 [37 \pm 12; n.a.] rMTLE = 6 [34 \pm 11; n.a.] HC = 15 [n.a. \pm n.a.; 6:9]	ER
Bauer et al., 2019 [85]	TLE = 17 [38.2 \pm 14.8; 9:8] HC = 51 [36.8 \pm 10.9; 25:26]	ER, ToM
Benuzzi et al., 2004 [86]	IMTLE = 5 [30.4 \pm 7.2; 3:2] rMTLE = 8 [35.7 \pm 7.2; 4:4] HC = 14 [n.a. \pm n.a.; 7:7] (age range 21–27 years)	ER
Bonora et al., 2011 [59]	MTLE = 41 [48.05 \pm 11.50; 17:24] HC = 50 [34.9 \pm 9.18; 20/30]	ER
Boucher et al., 2015 [60]	ATL = 15 [38.7 \pm 10.3; 7:8] IR = 15 [37.6 \pm 8.6; 6:9] HC = 20 [36.1 \pm 10.2; 10:10]	ER, ToM
Brierley et al., 2004 [61]	ATL = 28 [37.4 \pm n.a.; 12:16] HC = 32 [n.a.]	ER
*Broicher et al., 2012a [18]	MTLE = 28 [34.43 \pm 13.25; 12:16] HC = 29 [33.69 \pm 10.94; 13:16]	ER, ToM
Broicher et al., 2012b [97]	MTLE = 28 [37.43 \pm 12.60; 11:17] HC = 18 [31.22 \pm 5.81; 6:12]	ToM
Carvajal et al., 2009 [62]	ITL = 20 [35.4 \pm 9.6; 10:10] rTL = 23 [35 \pm 12.1; 10:13] HC = 43 [53.7 \pm 14.9; 20:23]	ER
Cohn et al., 2015 [63]	ITLE = 24 [38.9 \pm 11.9; 13:11] rTLE = 26 [38 \pm 13.7; 14:12] IATL = 18 [42.5 \pm 12.9; 11:7] rATL = 19 [38.9 \pm 9.6; 7:12] HC = 15 [38.3 \pm 8.6; 5:10]	ER, ToM
Glogau et al., 2004 [64]	MTLE = 28 [37.43 \pm 12.6; 11:17] HC = 18 [31.22 \pm 5.81; 6:12]	ER
Giovagnoli et al., 2009 [92]	TLE = 21 [39.67 \pm 14.41; 11:10] HC = 21 [41.81 \pm 16.7; 8:13]	ToM

Table 1 (continued)

References	Sample characteristics Group size [mean age \pm SD; Male:Female]	Social cognition: subfunction
*Giovagnoli et al., 2011 [101]	ITLE = 62 [35.96 \pm 11.64; 24:38] rTLE = 47 [38.33 \pm 10.64; 20:27] HC = 69 [52.03 \pm 17.04; 29:40]	ToM
*Giovagnoli et al., 2013 [42]	TLE = 54 [37.80 \pm 9.20; 26:28] HC = 42 [n.a. \pm 12.61; 18:24] (age range 40–64)	ToM
Giovagnoli et al., 2016 [98]	eTLE = 31 [31.87 \pm 9.4; 19:12] ITLE = 54 [34.91 \pm 10.23; 33:21] HC = 40 [36.05 \pm 9.64; 29:11]	ToM
Giovagnoli et al., 2020 [99]	TLE = 50 [40.8 \pm 12.98; 19:31] HC = 50 [39.20 \pm 13.32; 21:29]	ToM
Gomez-Ibanez et al., 2014 [65]	MTLE = 19 [41.9 \pm 10.6; 8:11] HC = 23 [37.3 \pm 10.7; 7:16]	ER
Gosselin et al., 2011 [66]	TL = 14 [42.1 \pm n.a.; 8:8] HC = 16 [n.a.]	ER
Hennion et al., 2015a [100]	TLE = 50 [42.4 \pm 11.82; 23:27] HC = 50 [42.81 \pm 12.46; 23:27]	ToM
Hennion et al., 2015b [67]	TLE = 50 [42.4 \pm 11.82; 23:27] HC = 50 [42.81 \pm 12.46; 23:27]	ER
Hennion et al., 2016 [93]	rMTLE = 12 [42.09 \pm 12.62; 8:4] IMTLE = 13 [42.54 \pm 9.6; 6:7] HC = 25 [42.5 \pm 12.3; 14:11]	ToM
Hlobil et al., 2008 [68]	r/preATL = 24 [28.8 \pm 11.4; 10:14] l/preATL = 12 [29.5 \pm 7.4; 3:9] r/postATL = 21 [33.4 \pm 10.5; 10:11] l/postATL = 19 [30.1 \pm 11.7; 9:10] HC = 28 [31.1 \pm 12.3; 17:11]	ER
Huang et al., 2020 [69]	MTLE-TLS = 20 [52.3 \pm n.a.; 12:8] HC = 12 [54.7 \pm n.a.; 5:7]	ER
Li et al., 2013 [94]	ITLE = 11 [37.55 \pm 14.7; 5:6] rTLE = 13 [43.31 \pm 11.83; 8:5] bTLE = 7 [46.14 \pm 13.07; 5:2] HC = 24 [37.75 \pm 16.77; 13:11]	ToM
McClelland et al., 2006 [75]	(l/e)ATL = 12 [30.3 \pm n.a.; n.a.] HC = 10 [30.4 \pm n.a.; 5:5]	ER
Meletti et al., 2003 [41]	MTLE = 33 [36.1 \pm 10.6; 13:20] TLE = 30 [35.8 \pm 10.7; 12:18] HC = 50 [34, n.a.; 18:32]	ER
Meletti et al., 2009 [70]	MTLE = 140 [38.6 \pm 9.9; 63:77] TLE = 36 [37.1 \pm 11.6; 16:20] HC = 50 [34.9 \pm 9.1; 20:30]	ER
Meletti et al., 2014 [71]	ATL = 42 [45.3 \pm 11.3; 25:17] HC = 39 [44 \pm 11.5; 22:17]	ER
Okruszek et al., 2017 [95]	MTLE = 31 [30.9 \pm 7.7; 14:17] HC = 47 [32.3 \pm 9.1; 25:22]	ToM
Palermo et al., 2010 [72]	ITL = 7 [46 \pm 10; 1:6] rTL = 8 [44.6 \pm 6; 3:5] HC = 13 [43 \pm 13; 7:6]	ER

Table 1 (continued)

References	Sample characteristics Group size [mean age \pm SD; Male:Female]	Social cognition: subfunction
*Realmuto et al., 2015 [88]	TLE = 21 [37 \pm 12.5; 8:13]	ER, ToM
*Reynders et al., 2005 [89]	HC = 21 [31.95 \pm 11.54; 12:9] IF-TLE = 13 [39.23 \pm 9.72; 8:5] TLE = 14 [39.57 \pm 12.36; 7:7] HC = 12 [39.92 \pm 12.87; 6:6]	ER
Rotshtein et al., 2010 [76]	aMTLE = 7 [34.5 \pm n.a.; 3:4] MTLE = 10 [37.7 \pm n.a.; 5:5] HC = 13 [31.6 \pm n.a.; 6:7]	ER
*Schacher et al., 2006 [43]	MTLE = 27 [36.5 \pm 10.7; 13:14] HC = 12 [33.8 \pm 12.4; 7:5]	Schacher
Sedda et al., 2013 [73]	rTLE = 24 [35.33 \pm 11.06; 14:10] lTLE = 32 [38.31 \pm 12.11; 18:14] HC = 54 [35.7 \pm 11.35; 23:31]	ER
Shaw et al., 2007 [74]	rATL = 10 [41 \pm 9; 5:5] lATL = 9 [33 \pm 11; 3:6] HC = 19 [33 \pm 11; 6:13]	ER, ToM
Szaflarski et al., 2014 [77]	lTLE = 34 [41 \pm 12; 7:27] HC = 30 [39 \pm 11; 8:22]	ER
Szaflarski et al., 2018 [78]	TLE = 12 [40 \pm 12; 2:10] HC = 24 [36 \pm 11; 4:20]	ER
Tanaka et al., 2013 [79]	MTLE = 63 [41.5 \pm n.a.; 32:31] postTL = 25 [43 \pm n.a.; 9:16] HC = 32 [33 \pm n.a.; 7:25]	ER
Walpole et al., 2008 [80]	TLE = 16 [45.31 \pm 11.81; 9:7] HC = 14 [43.86 \pm 10.92; 6:8]	ER
Wang et al., 2015 [96]	TLE = 67 [32.19 \pm 10.22; 36:31] HC = 30 [33.4 \pm 9.57; 16:14]	ToM
Wendling et al., 2015 [81]	SAH = 27 [41.38 \pm 8.3; 10:17] ATL = 33 [40.12 \pm 9.12; 17:16] HC = 30 [40.58 \pm 4.78; 15:15]	ER

Asterisks indicate that the study additionally included either FLE or eTLE/eFLE patients and was therefore included in the corresponding subgroup in the statistical meta-analysis.

Abbreviations: (A/r/l/pre/post) (l/e) TL (Anterior/right/left/pre-/postsurgical) (late/early onset) Temporal Lobectomy, HC Healthy Control group, IR Insula surgery, n. a. data not available, (b/l/r) (pre/post) (e/l) (a) (M) (IF) TLE (bilateral/left/right) (pre-/postsurgical) (early/late onset) (with structural amygdala damage) (Mesial) (with Ictal Fear) Temporal Lobe Epilepsy, SAH Selective Amygdalohippocampectomy, TLS Temporal Lobe Surgery

Results

Emotion recognition

ER was significantly impaired across subgroups compared to HCs ($d=0.80$, 95% CI 0.66-0.93, $Z=11.79$, $p<0.001$). Heterogeneity was significant ($I^2=52.4\%$, $Q=71.42$, $p<0.001$). TLE ($d=0.81$, $Z=11.01$, $p<0.001$) as well as eTLE/eFLE ($d=0.67$, $Z=4.43$, $p<0.001$) patients were significantly impaired compared to HCs. Although the TLE subgroup shows a numerically larger effect size than the eTLE/eFLE subgroup, the subgroup-analysis comparing TLE to eTLE/eFLE did not reveal a statistically significant difference ($\chi^2_{df=1}=1.10$,

$p=0.294$). The heterogeneity within the subgroups was significant for TLE ($I^2=55.33$, $Q=67.16$, $p<0.001$) but not for eTLE/eFLE ($I^2=5.11\%$, $Q=3.16$, $p=0.367$). For an overview see Fig. 2 (forest plot). Due to the low number of studies in the eTLE/eFLE subgroup, these results should be interpreted with caution. The single study comparing FLE patients with HC yielded an effect size of $d=1.70$ (95% CI 0.83-2.57), with FLE patients performing significantly worse than HCs [90].

Visual inspection of the Funnel Plot, Galbraith Plot, Normal Quantile Plot and the Standardized Residual Histogram does not clearly indicate the presence

Table 2 Sample characteristics of studies comparing FLE patients *versus* HC

References	Sample characteristics Group size [mean age \pm SD; Male:Female]	Social cognition subfunction
Farrant et al., 2005 [90]	FLE = 14 [34.36 \pm 12.05; 6:8] HC = 14 [35.79 \pm 9.91; 6:8]	ER, ToM
Giovagnoli et al., 2011 [101]	FLE = 29 [35.77 \pm 12.53; 11:18] HC = 69 [52.03 \pm 17.04; 29:40]	ToM
Giovagnoli et al., 2013 [42]	FLE = 12 [37.17 \pm 13.41; 6:6] HC = 42 [n.a. \pm 12.61; 18:24] (age range: 40–64 y.)	ToM
Giovagnoli et al., 2020 [102]	FLE = 14 [34.36 \pm 12.05; 6:8] HC = 14 [35.79 \pm 9.91; 6:8]	ToM
Javor et al., 2019 [103]	FLE = 15 [36 \pm 8.10; 7:8] HC = 15 [34.07 \pm 6.05; 7:8]	ToM

Abbreviations: n.a. data not available

Table 3 Sample characteristics of studies comparing eTLE/eFLE patients *versus* HC

References	Sample characteristics Group size [mean age \pm SD; Male:Female]	Social cognition subfunction
Broicher et al., 2012a [18]	eTLE/eFLE = 14 [33.36 \pm 11.74; 10:4] HC = 29 [33.69 \pm 10.94; 13:16]	ER, ToM
Giorgi et al., 2016 [104]	JME = 20 [26.7 \pm 6.6; 2:18] HC = 20 [26.2 \pm 5.8; 2:18]	ToM
Hu et al., 2016 [87]	eTLE/eFLE = 43 [17.72 \pm 5.26; 27:16] HC = 60 [17.18 \pm 5.17; 40:20]	ER, ToM
Morou et al., 2018 [105]	GE = 35 [29.9 \pm 11.5; 8:27] HC = 70 [32.6 \pm 10.99; 43:27]	ToM
Realmuto et al., 2015 [88]	IGE = 18 [26.3 \pm 7.2; 6:12] HC = 21 [31.95 \pm 11.54; 12:9]	ER, ToM
Reynders et al., 2005 [89]	IGE = 10 [32.9 \pm 19.31; 4:6] HC = 12 [39.92 \pm 12.87; 6:6]	ER
Schacher et al., 2006 [43]	eTLE/eFLE = 27 [35.9 \pm 12.8; 13:14] HC = 12 [33.8 \pm 12.4; 7:5]	ToM

Abbreviations: IGE Idiopathic Generalized Epilepsy, GE Generalized Epilepsy, JME Juvenile Myoclonic Epilepsy

of publication bias in the TLE subgroup. The Egger Regression *t*-test ($t = -0.96$, $p = 0.346$) indicated the absence of severe publication bias [108]. The Failsafe-*N* as supposed by Rosenthal [109] also did not indicate the presence of publication bias (Failsafe-*N* = 3127) in the TLE subgroup. Due to the small number of studies, no conclusions can be drawn regarding the presence of publication bias in the eTLE/eFLE subgroup.

Five studies included in the meta-analysis reported statistical comparisons of different types of epilepsy groups regarding ER. A descriptive inspection of effect sizes and *p*-values revealed a tendency of TLE patients

performing worse in ER tasks than eTLE/eTLE patients [18, 88, 89]. No studies reported comparisons between FLE and eTLE/eFLE patients or between TLE and eTLE/eFLE patients. For further details, see Table 4.

Theory of mind

ToM was significantly impaired across subgroups compared to HCs ($d = 0.87$, 95% CI 0.71–1.03, $Z = 11.00$, $p < 0.001$). Heterogeneity was significant ($I^2 = 53.18\%$, $Q = 53.40$, $p = 0.001$). ToM was significantly impaired in TLE ($d = 0.92$, $Z = 8.64$, $p < 0.001$) as well as FLE ($d = 1.16$, $Z = 24.43$, $p < 0.001$) and eTLE/eFLE

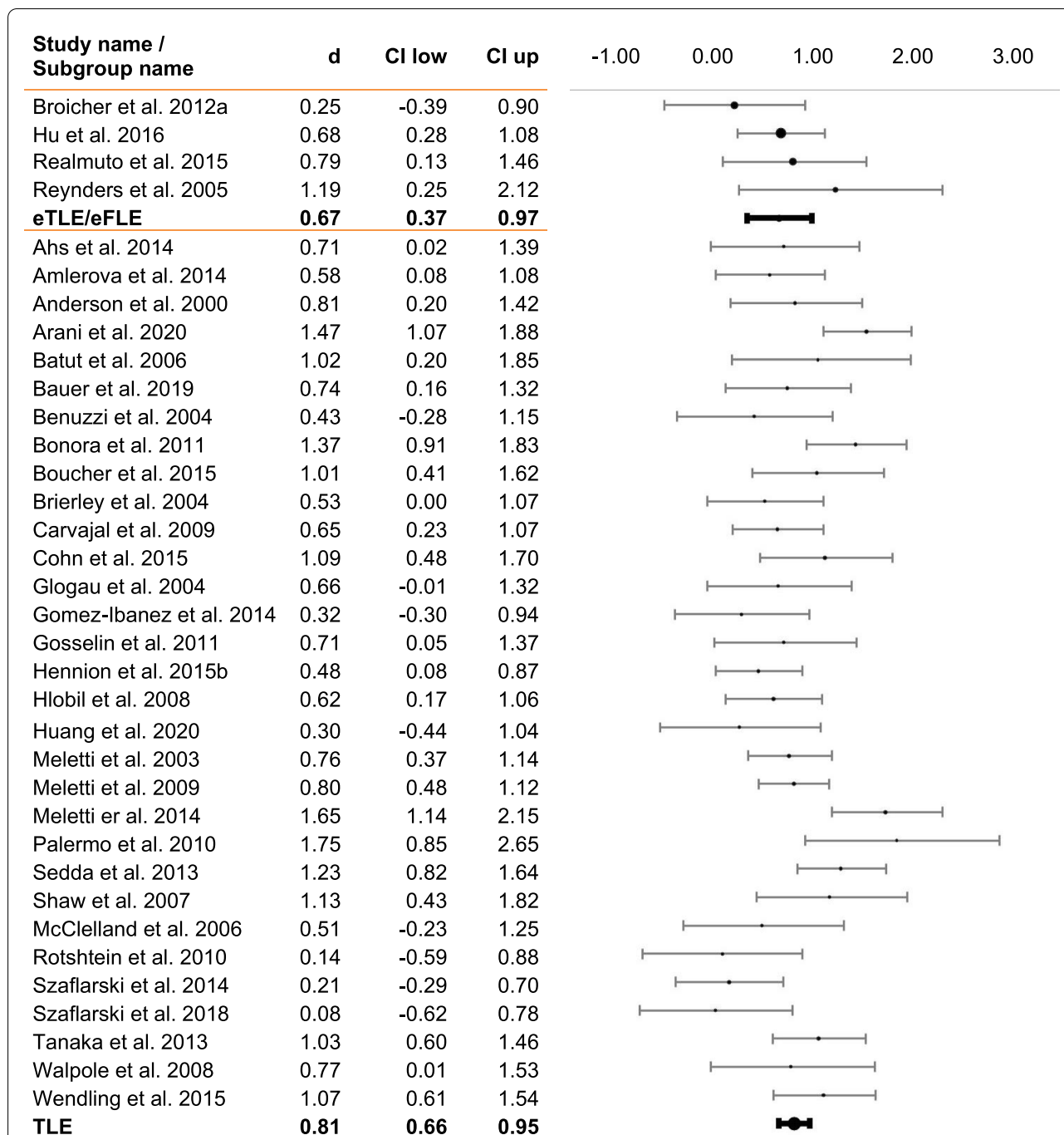


Fig. 2 Forest plot of individual and mean weighted effect sizes (*Hedge's g = d*) for ER in patients with TLE and eTLE/eFLE in comparison to HC. Abbreviations: CI low, lower limit of the 95% confidence interval; CI up, upper limit of the 95% confidence interval

($d = 0.55$, $Z = 3.49$, $p < 0.001$) patients compared to HCs. The between-group heterogeneity across all subgroups was significant ($Q_{bet} = 14.94$, $p < 0.001$). Post-hoc comparisons revealed that TLE and FLE patients had significantly more impaired ToM than eTLE/eFLE patients (TLE vs eTLE/eFLE: $\chi^2_{df=1} = 8.7$, $p = 0.003$;

FLE vs eTLE/eFLE: $\chi^2_{df=1} = 13.77$, $p < 0.001$). No statistically significant difference was found between TLE and FLE patients ($\chi^2_{df=1} = 2.76$, $p = 0.097$). There was no evidence for significant heterogeneity within groups for eTLE/eFLE ($I^2 = 40.50\%$, $Q = 8.40$, $p = 0.135$) and FLE ($I^2 = 0.00\%$, $Q = 0.57$, $p = 0.966$), except for the

Table 4 Results of studies comparing epilepsy subgroups

References	Subfunction: group comparison	Results	Effect size <i>d</i> (= hedge's <i>g</i>), [95% CI]
Broicher et al., 2012a [18]	ER: TLE vs eTLE/eFLE	TLE patients performed significantly worse than the eTLE/eFLE group in the sub-score Emotion Recognition Quotient of the comprehensive affect testing system (CATS) without further significant differences (tendency: TLE < eTLE/eFLE)	<i>d</i> = 0.50 [-0.16; 1.16]
	ToM: TLE vs eTLE/eFLE	No significant differences among the tasks between TLE and eTLE/eFLE patients (tendency: TLE < eTLE/eFLE)	<i>d</i> = 0.48 [-0.17; 1.15]
Realmuto et al., 2015 [88]	ER: TLE vs eTLE/eFLE	No significant differences between TLE and eTLE/eFLE patients (tendency: TLE > eTLE/eFLE)	<i>d</i> = -0.04 [-0.68; 0.60]
	ToM: TLE vs eTLE/eFLE	No significant differences between TLE and eTLE/eFLE (tendency: TLE < eTLE/eFLE)	<i>d</i> = 0.20 [-0.44; 0.84]
Reynders et al., 2005 [89]	ER: TLE vs eTLE/eFLE	TLE patients with "ictal fear", but not those without "ictal fear", performed significantly worse in the recognition of fear test in comparison to the eTLE/eFLE group, without further significant differences (recognition of basic emotions)	<i>d</i> = 0.42 [-0.33; 1.16]
Schacher et al., 2006 [43]	ToM: TLE vs eTLE/eFLE	Patients with TLE performed significantly worse than those with eTLE/eFLE	n.a.
Giovagnoli et al., 2011 [101]	ToM: FLE vs TLE	FLE patients had significantly impaired social faux-pas recognition compared to TLE patients	<i>d</i> = 0.31 [-0.10; 0.72]
Giovagnoli et al., 2013 [42]	ToM: FLE vs TLE	Numerically, TLE performed worse than FLE patients, although the differences were not statistically significant	<i>d</i> = -0.11 [-0.74; 0.52]

Abbreviations: n. a. data not available

TLE group ($I^2 = 52.52\%$, $Q = 29.49$, $p = 0.009$). Again, the results should be interpreted with caution due to the small sample sizes in the eTLE/eFLE and FLE subgroups. For an overview see Fig. 3 (forest plot).

Visual inspection of the Funnel Plot, Galbraith Plot, Normal Quantile Plot, the Standardized Residual Histogram, and the Failsafe-N (Failsafe- $N = 984$) proposed by Rosenthal [109] did not indicate the presence of publication bias in the TLE subgroup. Due to the small number of studies, no conclusion can be drawn regarding the presence of publication bias in the eTLE/eFLE and the FLE subgroups.

Five studies included in the meta-analysis reported statistical comparisons of ToM between different types of epilepsy. A descriptive inspection of effect sizes and p -values revealed that TLE patients tend to perform worse in ToM tasks than eTLE/eTLE patients [18, 43, 88]. No clear trend was found from the comparison between FLE and TLE patients [42, 101], while no study reported a comparison between FLE and eTLE/eFLE patients. For further details, see Table 4.

The assessment of emotion recognition in epilepsy

The paradigms used for the assessment of emotion recognition in epilepsy research can be roughly categorized into three types with regards to the modality. The vast majority of studies used facial emotion

recognition paradigms [110–116] predominantly by using stimulus material from the Ekman & Friesen series of static pictures [110]. Only a small number of studies utilized task paradigms with prosodic emotion recognition [117–120] and tasks for affect recognition in emotionally expressive gaits and postures [121] to assess emotion recognition. Regarding the presentation of the stimuli, there are a broad variety of presentation methods and assessment designs, most specifically designed for individual studies. These included, for example, morphed pictures of the Ekman & Friesen series [66] and selective presentation of a subset of basic emotions [58, 86]. Only a small number of studies used more comprehensive batteries [54, 122–124]. For more detailed information see Table 5.

The assessment of theory of mind in epilepsy

The most commonly used task in the assessment of ToM in epilepsy is the Faux Pas Test, a text-based task in which participants are required to make ToM inferences in stories about social faux pas [125]. Other commonly used tasks include the Reading the Mind in the Eyes test [126], in which participants are required to infer mental states based on photographs of the eye region of faces, and the Frith-Happé Animations [127, 128], in which participants are required to attribute mental states to moving geometric shapes. Other paradigms are rarely used, including the inference of mental states based on cartoons [129,

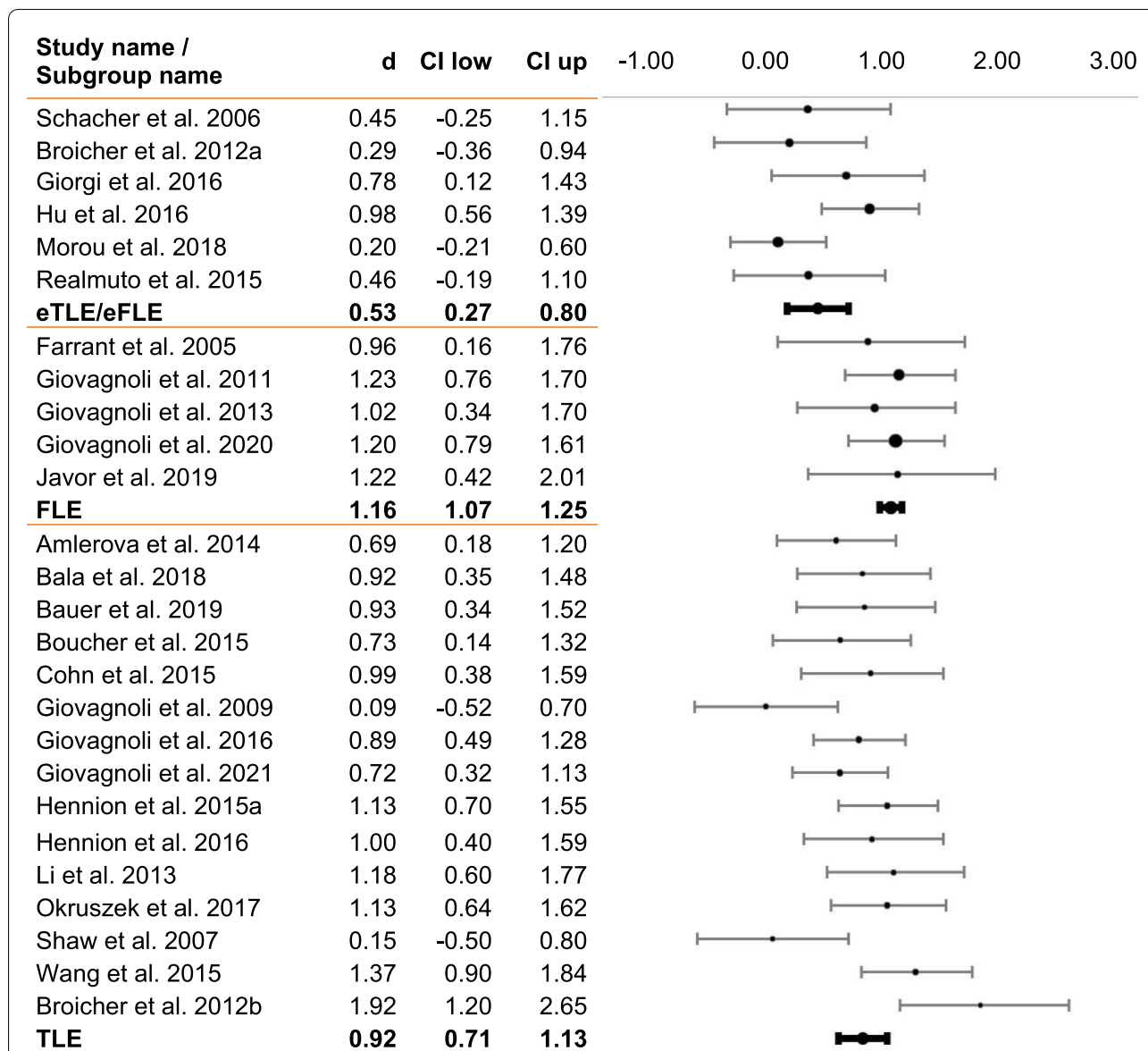


Fig. 3 Forest plot of individual and mean weighted effect sizes (*Hedge's g = d*) for ToM in patients with TLE, FLE and eTLE/eFLE in comparison to HC. Abbreviations: CI low, lower limit of the 95% confidence interval; CI up, upper limit of the 95% confidence interval

130], short stories [131], movies [132], the recognition/comprehension of irony [54], sarcasm [100], metaphor and hinting [105]. Again, the use of comprehensive test batteries is rare [54, 124]. For an overview see Table 6.

Discussion

Social cognition in epilepsy

In this meta-analytic review, we demonstrated that ER is impaired in TLE and eTLE/eFLE patients and ToM is impaired in TLE, FLE and eTLE/eFLE patients. There are no significant differences in ER performance between

TLE and eTLE/eFLE patients, although a declarative review of reported within-study comparisons revealed a trend of TLE patients performing worse than eTLE/eFLE patients in ER; and there is also no significant difference in ToM between FLE and TLE patients. There are significant differences in ToM ability between eTLE/eFLE and FLE as well as between eTLE/eFLE and TLE patients, with less pronounced deficits in eTLE/eFLE. Due to the small number of studies comparing eTLE/eFLE and FLE, the results should be interpreted with caution. While there is a growing number of studies on

Table 5 Assessment tools for ER in the primary studies included in this meta-analysis

Paradigm	Subgroup	Number of Studies k , epilepsy patients N_E and control subjects N_{HC}	Effect size d (= Hedge's g), [CI 95%]
Ekman & Friesen Pictures of Facial Affect	TLE	$k = 19, N_E = 764, N_{HC} = 553$	$d = 1.07$ [0.60; 1.54]
	FLE	$k = 1, N_E = 14, N_{HC} = 14$	$d = 1.83$ [0.92; 2.74]
	eTLE/eFLE	$k = 3, N_E = 71, N_{HC} = 93$	$d = 0.81$ [0.25; 1.38]
NimStim Set of Facial Expressions	TLE	$k = 3, N_E = 90, N_{HC} = 109$	$d = 0.34$ [-0.21; 0.90]
	Comprehensive Affect Testing System	TLE	$k = 1, N_E = 28, N_{HC} = 29$
Dynamic Facial Expressions	eTLE/eFLE	$k = 1, N_E = 14, N_{HC} = 29$	$d = 0.25$ [-0.39; 0.90]
	TLE	$k = 1, N_E = 88, N_{HC} = 32$	$d = 1.03$ [0.60; 1.46]
Florida Affect Battery	TLE	$k = 1, N_E = 52, N_{HC} = 43$	$d = 0.65$ [0.23; 1.07]
The Awareness of Social Inference Test part 1	TLE	$k = 1, N_E = 50, N_{HC} = 15$	$d = 1.09$ [0.48; 1.70]
Montreal Affective Voices	TLE	$k = 1, N_E = 50, N_{HC} = 50$	$d = 0.44$ [0.04; 0.84]
Emotional Prosody Recognition Battery	TLE	$k = 1, N_E = 41, N_{HC} = 50$	$d = 0.83$ [0.40; 1.27]
Vocal Expressions of Emotion	TLE	$k = 1, N_E = 25, N_{HC} = 32$	$d = 0.48$ [-0.05; 1.02]
Emotionally Expressive Gaits	TLE	$k = 1, N_E = 20, N_{HC} = 11$	$d = 0.30$ [-0.44; 1.04]
Radboud Face Database	TLE	$k = 1, N_E = 17, N_{HC} = 51$	$d = 0.60$ [0.04; 1.17]
STOIC Dynamic Facial Emotional Expressions Database	TLE	$k = 1, N_E = 17, N_{HC} = 51$	$d = 0.91$ [0.34; 1.49]
Berlin Database of Emotional Speech	TLE	$k = 1, N_E = 17, N_{HC} = 51$	$d = 0.52$ [-0.03; 1.09]
3-Dimensional Facial Expressions Database	TLE	$k = 1, N_E = 15, N_{HC} = 13$	$d = 1.75$ [0.85; 2.65]
Karolinska's Facial Affect Pictures	TLE	$k = 1, N_E = 12, N_{HC} = 15$	$d = 1.02$ [0.20; 1.85]

social cognition in TLE, there is still a paucity of studies on FLE and eTLE/eFLE patients, especially regarding ER. More studies are needed, particularly to identify specific eTLE/eFLE pathologies and disorders with higher risks of socio-cognitive impairment.

Although cognitive domains including attention, memory, and executive functioning have been found to be impaired in epilepsy, few studies have addressed the impairment in the context of social cognition [133]. It has been argued by several authors that the neurocognitive deficits may contribute to impairment of social cognition in epilepsy patients, for example, deficits in executive functions in patients with idiopathic generalized epilepsies [134]. To date, there is a paucity of research on this subject. Current research presents conflicting evidence on a relationship between general intelligence and emotion recognition in TLE [50]. It is argued that deficits in social cognition are independent of intellectual disability in epilepsy [135], and that there is no formal correlation between ToM and general intelligence in epilepsy patients [48]. Others have pointed out conflicting evidence for a correlation between IQ and ToM, while there is no evidence for a significant correlation between verbal IQ and ToM in epilepsy patients [48]. Furthermore, it has been pointed out that although there is evidence for impaired executive functioning in epilepsy subgroups such as TLE, most studies have failed to identify correlations between executive functions and social

cognition in patients with idiopathic generalized epilepsy [48, 134]. Due to the paucity of research and conflicting evidence regarding the relationship between neurocognitive functions, general cognitive ability and social cognition, cognitive deficits may nevertheless play a role in the associated impairments of social cognition and may have confounded the current as well as previous meta-analytic reviews in this field. The discrepancies of the results among studies, as well as the high level of heterogeneity in social cognition within subgroups in this meta-analysis, may be due to the variety of tests used to measure social cognition, as well as the variety of patients included in the primary studies (for example, heterogeneity regarding disease- and patient-related variables, selective samples of subgroups such as TLE patients after amygdalo-hippocampectomy, or patients with idiopathic generalized epilepsies in the eTLE/eFLE subgroup). This prevents accurate comparison between results and limits the reproducibility.

A limitation of this meta-analysis is the lack of inclusion of potentially relevant covariates such as the subtype and etiology of the epileptic syndrome – especially with regard to the very broadly defined and etiologically diverse subgroup of eTLE/eFLE patients – age at seizure onset, seizure laterality, history of febrile seizures, seizure frequency, history of brain surgery, duration of epilepsy, and pharmacological therapy. These variables tend to be underreported in primary studies.

Table 6 Assessment tools for ToM in the primary studies included in this meta-analysis

Paradigm	Subgroup	Number of Studies k , epilepsy patients N_E and control subjects N_{HC}	Effect size d (= Hedge's g), [95% CI]
Faux Pas Test	TLE	$k = 13, N_E = 613, N_{HC} = 456$	$d = 1.03$ [0.68; 1.37]
	FLE	$k = 4, N_E = 130, N_{HC} = 167$	$d = 1.14$ [1.00; 1.28]
	eTLE/eFLE	$k = 3, N_E = 76, N_{HC} = 111$	$d = 0.24$ [0.07; 0.40]
Reading the Mind in the Eyes Test	TLE	$k = 3, N_E = 74, N_{HC} = 96$	$d = 0.71$ [0.25; 1.17]
	FLE	$k = 2, N_E = 29, N_{HC} = 29$	$d = 1.13$ [0.89; 1.37]
	eTLE/eFLE	$k = 2, N_E = 57, N_{HC} = 89$	$d = 0.69$ [0.02; 1.35]
Frith-Happé Animations (Moving Triangles)	TLE	$k = 3, N_E = 93, N_{HC} = 74$	$d = 0.70$ [0.06; 1.34]
	eTLE/eFLE	$k = 1, N_E = 14, N_{HC} = 29$	$d = 0.20$ [-0.45; 0.84]
Happé Strange Stories Test	TLE	$k = 2, N_E = 98, N_{HC} = 54$	$d = 1.41$ [0.57; 2.24]
	FLE	$k = 1, N_E = 14, N_{HC} = 14$	$d = 0.44$ [-0.32; 1.21]
False Belief Test	TLE	$k = 2, N_E = 98, N_{HC} = 54$	$d = 1.05$ [0.55; 1.55]
Happé Cartoon Task	TLE	$k = 1, N_E = 31, N_{HC} = 24$	$d = 1.28$ [0.69; 1.87]
	FLE	$k = 1, N_E = 14, N_{HC} = 14$	$d = 0.93$ [0.13; 1.72]
Story-Based Empathy Task	TLE	$k = 1, N_E = 21, N_{HC} = 21$	$d = 0.78$ [0.16; 1.43]
	eTLE/eFLE	$k = 1, N_E = 18, N_{HC} = 21$	$d = 0.47$ [-0.18; 1.11]
Visual Cartoon Task	TLE	$k = 1, N_E = 67, N_{HC} = 30$	$d = 1.76$ [1.24; 2.23]
The Awareness of Social Inference Test part 2 & 3	TLE	$k = 1, N_E = 50, N_{HC} = 15$	$d = 0.99$ [0.38; 1.59]
Sarcasm Comprehension	TLE	$k = 1, N_E = 50, N_{HC} = 50$	$d = 1.01$ [0.60; 1.44]
Action Comprehension	TLE	$k = 1, N_E = 50, N_{HC} = 50$	$d = 0.92$ [0.52; 1.35]
Yoni Task	eTLE/eFLE	$k = 1, N_E = 43, N_{HC} = 60$	$d = 0.06$ [-0.34; 0.45]
Comprehension of Hinting Test	eTLE/eFLE	$k = 1, N_E = 35, N_{HC} = 70$	$d = 0.27$ [-0.14; 0.68]
Comprehension of Sarcasm and Metaphor	eTLE/eFLE	$k = 1, N_E = 35, N_{HC} = 70$	$d = 0.49$ [0.08; 0.91]
Visual ToM Tasks	eTLE/eFLE	$k = 1, N_E = 35, N_{HC} = 70$	$d = 0.35$ [-0.06; 0.76]
Networks of Emotional Processing (NEmo Battery): Recognition of Irony	TLE	$k = 1, N_E = 17, N_{HC} = 51$	$d = 0.74$ [0.17; 1.30]
Movie for the Assessment of Social Cognition	TLE	$k = 1, N_E = 17, N_{HC} = 51$	$d = 1.49$ [0.88; 2.10]

In particular, early seizure onset seems to be associated with more severe impairment in ToM and ER in epilepsy patients [49, 51, 135], as well as longer duration of disease [50, 135]. Furthermore, there is a tendency for more severe ER and ToM deficits in right-sided TLE compared to left-sided TLE [51, 52]. Systematic reviews suggest no relevant differences between TLE patients with or without as well as pre- and post-temporal lobectomy surgery regarding social cognition [50, 51]. There is still a paucity of research and conflicting evidence regarding the effects of pharmacological therapy on social cognition in epilepsy patients [50, 136].

Assessment tools in clinical practice and research

Ecological validity

The most common approach to testing ER in epilepsy research is to label photographs of static facial expressions of basic emotions [54] in a variety of ways (matching tasks, labeling tasks, etc.). Such tasks do not correspond with the dynamic visuo-spatial and temporal information

in faces processed in everyday social interactions [55] and do not reflect the multimodality of everyday emotion recognition [1, 54], including body movement, prosody, verbal information and context. Regarding ToM, the most commonly used assessment tools in epilepsy research are too artificial in nature (short stories, cartoons, static pictures of eyes, moving triangles) and/or assess narrowly defined sub-processes (e.g. faux-pas detection), which limit their ecological validity [54].

Economic viability / usability in clinical practice

Many of the assessment tools that lack ecological validity are often well suited for clinical practice with regard to the complexity and duration of application. However, due to their lack of ecological validity and narrow scope regarding socio-cognitive subprocesses, it is necessary to use multiple tools to achieve a more comprehensive assessment. Accordingly, attempts to construct ecologically valid assessment tools, such as the Movie for the Assessment of Social Cognition (MASC) [132] and more comprehensive batteries, such as the NEmo battery

(Networks of Emotion Processing) [54], CATS (comprehensive affect testing system) [122], and TASIT (The Awareness of Social Inference Test) [124], result in longer administration times, which are often too long for everyday clinical neuropsychological practice.

Attempts to provide new and apply existing more ecologically valid and/or economically viable assessment tools for social cognition are scarce in clinical epilepsy research (e.g. [1, 53, 140]) as well as in other clinical populations [138].

Future directions

We recommend an increased effort in the development and use of multimodal, comprehensive, ecologically valid, economically viable assessment tools for social cognition in epilepsy research and clinical practice as well as in other clinical populations at risk of socio-cognitive impairment. We suggest two approaches for the development of new research tools: (a) short tests with high ecological validity and a broad integration of socio-cognitive subprocesses, (b) short screening tools for social cognition *via* the integration of parts of multiple established assessment tools in the manner of, for example, the Montreal Cognitive Assessment [137] for general cognitive function or Frontal Assessment Battery [139] for executive function.

Future studies that test multiple subfunctions in ER, ToM, general cognition, speed, attention, memory, and executive functions in the same population would be informative. Furthermore, larger longitudinal studies with a broad variety of relevant covariates would help advance our understanding of the effects of epilepsy duration, seizure frequency, age of epilepsy onset, effect of seizure freedom, and antiepileptic drugs on social cognition. The standardization of terminology and testing in the field of applied social cognition would enhance the reproducibility and comparability of results.

The difficulties with social interaction and functioning observed in some epilepsy patients may, at least in part, be due to an altered ability to interpret emotions or mental states. It appears that epilepsy patients may struggle more with subtle or nuanced expressions of emotion. Currently, it is unknown how the socio-cognitive deficits seen in some patients significantly affect diverse areas of life including employment, romantic and family relationships, and friendships. It is therefore important to quantify the functional burden of impaired social cognition in epilepsy to determine its specific clinical relevance in future studies.

Conclusions

Considering the importance of social skills in personal and economic success and QoL, the exclusion of social cognition from the canon of relevant functions investigated in epilepsy as well as the many other conditions affecting social cognition [5] can no longer be justified. A richer understanding of the nature of social cognition in epilepsy may help further characterize certain epilepsy syndromes, and facilitate development of therapeutic interventions to improve social abilities in these patients. Further studies on social cognition in epilepsy, especially in FLE and eTLE/eFLE, with the use of ecologically valid and diverse, multimodal assessment tools, are recommended. Further, there is a need for standardized, psychometrically sound, ecologically valid and economically viable assessment tools for social cognition in daily clinical practice with (but not limited to) epilepsy patients [140].

Abbreviations

eFLE/eTLE: Extra-temporal/extra-frontal epilepsy; ER: Emotion recognition; FLE: Frontal lobe epilepsy; QoL: Quality of life; TLE: Temporal lobe epilepsy; ToM: Theory of mind.

Acknowledgements

We thank Victoria Reed and Victoria Lyn Ives-Deliperi for their assistance with the current and previous versions of the manuscript. The project was supported by the Swiss Epilepsy Foundation.

Authors' contributions

ME: conception, design, systematic literature search, study extraction, screening for study eligibility, data extraction, data analysis, data interpretation, drafting; HJ: conception, designing, data interpretation, revision, approval. The author(s) read and approved the final manuscript.

Authors' information

Not applicable.

Funding

Not applicable (no funding was received).

Availability of data and materials

The datasets used during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

HJ is a member of the Editorial Board of *Acta Epileptologica*. HJ was not involved in the journal's review of, or decision related to this manuscript. The authors declare that they have no further competing interests.

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Received: 11 January 2022 Accepted: 6 April 2022
Published online: 10 June 2022

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