Neuroscience and Biobehavioral Reviews 121 (2021) 106–118

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Theory of mind in adults with traumatic brain injury: A meta-analysis

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ARTICLE INFO

Keywords:
Traumatic brain injury
Theory of mind
Meta-analysis

ABSTRACT

Studies of abnormal theory of mind (ToM) performance in adult patients with traumatic brain injury (TBI) have reported inconsistent results. Therefore, we conducted a meta-analysis to characterize ToM performance in adult patients with TBI. Random-effects models were employed to estimate the overall effect size and the differential effect sizes across different ToM aspects. Based on a sample of 28 studies (1031 patients and 865 healthy controls), the meta-analytic findings revealed that ToM was significantly impaired in adult patients with TBI compared to healthy controls (g = -1.13). Besides, patients with TBI showed significant impairments in individual ToM tasks, as well as for different stimulus modes and contents involved in these ToM tasks. A meta-regression indicated a positive association between ToM performance and Glasgow Coma Scale score. The results of the current meta-analysis suggest that the performance in ToM tasks may be a good predictor of functional outcomes in adults with TBI, which is important for the identification of targets for cognitive interventions and the development of useful training intervention programs.

1. Introduction

Traumatic brain injury (TBI) refers to head injuries that disrupt normal brain functions (Ghajar, 2000). The damage typically arises from a sudden acceleration-deceleration insult to the brain, such as during motor vehicle accidents, falls, sports injuries, or assaults. Currently, TBI is a major cause of mortality and disability worldwide (Hyder et al., 2007; Thornhill et al., 2000), with 10 million new cases annually (Langlois et al., 2006). Among TBI survivors, more than 43 % experience long-term disability (Corrigan et al., 2010). In addition, TBI commonly leads to a wide range of psychosocial function deficits (Eslinger et al., 1995; Green et al., 2008; Yates, 2003), which may result in a breakdown of social functioning, such as loss of employment, reduced social networks, and disruption to intimate relationships (Elsass and Kinsella, 1987; Hallett et al., 1994; Kersel et al., 2001; Oddy and Humphrey, 1980; Tate et al., 1989).

Although psychosocial functioning after TBI is influenced by many factors, a growing body of evidence shows that social cognitive skills are critical contributors (May et al., 2017; McDonald and Flanagan, 2004; Spikman et al., 2012). Social cognition can be defined as "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others" (Bora et al., 2015; Green et al., 2008), which is crucial for effective and adaptive interpersonal functioning and communication. One of the higher-level skills of social cognition is theory of mind (ToM), which is the ability to attribute mental states to others and to use these attributions to understand and predict behavior (Bora et al., 2015; Leppanen et al., 2018). As the ToM ability plays an important role in social cognition, ToM impairment is likely to lead to serious problems in psychosocial functioning (Bora and Pantelis, 2016; Bora et al., 2015; Yi et al., 2020).

Recently, a number of studies assessed ToM deficits in adult patients with TBI (Bivona et al., 2015; Bosco et al., 2018; Saint-Jean et al., 2019; Turkstra, 2008). However, there have been inconsistent findings. For

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https://doi.org/10.1016/j.neubiorev.2020.12.010
Received 2 July 2020; Received in revised form 27 October 2020; Accepted 8 December 2020
Available online 20 December 2020

example, Wilu Wilu et al. (Wilu Wilu et al., 2019) and Bivona et al. (Bivona et al., 2014) found that compared to healthy controls (HC), adult patients with TBI were significantly impaired in the First-Order False-Belief Test (FBT-1, one ToM task), whereas Muller et al. (Muller et al., 2010) and Stone et al. (Stone et al., 1998) found no difference in the FBT-1 between TBI patients and HC. These inconsistent findings might be related to low statistical power, as many of the available studies have small sample sizes. Moreover, the methods used to evaluate ToM performance varied across studies (Havet-Thomassin et al., 2006; Henry et al., 2006; Leppanen et al., 2018; May et al., 2017). Besides inconsistent findings, it is also not clear which particular ToM aspects such as mode (i.e., verbal vs. visual) and content (i.e., cognitive vs. affective) of the stimuli used in ToM tasks are impaired in adult TBI patients (Muller et al., 2010; Spikman et al., 2012; Theadom et al., 2019; Wilu Wilu et al., 2019). To answer these important clinical questions, a meta-analysis of the ToM findings published to date in adult patients with TBI was needed, which is helpful in increasing statistical power and refining conclusions from inconsistent findings of individual studies.

A prior meta-analysis was conducted to examine ToM differences between patients with acquired brain injury (ABI) and HC. However, this meta-analysis included only literature containing four specific ToM tasks (FBT-1, Second FBT [FBT-2], understanding indirect speech, and Faux Pas Test [FPT]) and included patients of different age groups. Moreover, the patients included in this meta-analysis were rather heterogeneous, and patients with TBI were not specifically investigated (Martin-Rodriguez and Leon-Carrion, 2010). Therefore, in the present study, we conducted a meta-analysis to better characterize ToM performance in adult patients with TBI. In addition, we conducted subgroup meta-analyses to investigate the impairment in different aspects of ToM tasks, including stimulus mode (verbal ToM and visual ToM), stimulus content (cognitive ToM and affective ToM), and individual ToM tasks. Furthermore, meta-regression analyses were performed to examine the effects of potential confounders such as age and disease duration on ToM deficits. Our meta-analysis will be helpful to understand the patterns of ToM function in adult patients with TBI, which may be important for the identification of targets for cognitive interventions and the development of useful training intervention programs.

2. Methods

The meta-analysis was registered with PROSPERO (ID CRD42020175560) and conducted according to a predetermined protocol.

2.1. Search selection

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline recommendations (Page and Moher, 2017). Electronic databases (including PubMed, Web of Science, and Embase) were searched from inception to March 2020. The search keywords used were ("theory of mind" OR "ToM" OR "social cognition" OR "mentalizing" OR "mentalising") AND ("traumatic brain injury" OR "TBI" OR "brain trauma" OR "closed head injury" OR "head injury" OR "head trauma" OR "prefrontal cortex damage"). In addition, other resources such as the references of all included studies were manually searched.

2.2. Inclusion criteria

Studies were included if they met the following five criteria: (1) should be published as peer-reviewed research articles in English, (2) had to include individuals with with TBI $\geq$ 18 years, (3) should assess ToM performance using standard ToM measures, (4) should include a matched HC group, and (5) should report sufficient data to calculate effect sizes and standard errors of ToM measures.

2.3. Exclusion criteria

Studies were excluded for the following four reasons: (1) if patient samples overlapped with another study with a larger sample size; (2) if they had a sample size $<$ 10 in each group to ensure the outcome reliability (Leppanen et al., 2018); (3) if they were not original research articles, such as a research protocol, letter, conference abstract, review, or editorial; and (4) if no sufficient data on ToM measures were available.

2.4. Screening, data extraction, and quality assessment

Two investigators independently conducted article retrieval, screening, data collection, and quality evaluation. The relevant data were extracted including the first author's family name, publication year, title, TBI diagnosis criteria, sample size, number of female participants, mean age, mean education level, Glasgow Coma Scale (GCS) score, individual ToM tasks used, as well as the data used for calculating effect sizes and standard errors of the ToM measures.

To assess study quality, a nine-star protocol was used based on the Newcastle-Ottawa Scale for case-control studies. Studies with $\geq$ 7 stars were considered high-quality (Stang, 2010).

2.5. ToM measures

2.5.1. Individual ToM tasks

Table 1 summarizes the different individual ToM tasks used, most commonly RMET (to assess understanding of other people's mental states from the eyes) (Baron-Cohen et al., 2001) and FPT (to recognize *faux pas* in series of short stories) (Baron-Cohen et al., 1999); other tasks included, different FBT (FBT-1, FBT-2, to probe the belief of one of the characters in stories) (Bach et al., 1998; Frith and Corcoran, 1996; Rowe et al., 2001), Strange Stories Test (SST, to assess comprehension of the characters' mental states in stories) (Happé, 1995), Cartoon Test (CT, attribution of mental states to characters in cartoon pictures) (Happe et al., 1999), Cartoon Predictions Test (CPT, to make inferences regarding the characters' feelings and intentions in a cartoon picture) (May et al., 2017), Video Social Inference Test (VSIT, to test social inference based on a video-based task) (Turkstra and Lyn, 2000), Hinting Test (HT, to assess understanding of people's intentions from indirect messages) (Corcoran et al., 1995), The Awareness of Social Inference Test (TASIT, including TASIT Part 2 and TASIT Part 3, to make social inferences from video clips and vignettes) (McDonald et al., 2014), Moving Shapes Test (MST, to make inferences based on the 12 silent animated movies) (Abell et al., 2000), Assessment of Social Context Task (ASC, to make inferences by using videotaped stimuli of everyday interactions) (Hynes et al., 2011), Character Intentions Task (CIT, to make inferences regarding the characters' intentions in 20 short comic strips) (Brunet et al., 2000), Interpretative Diversity Test (IDT, to make inferences from four line drawing pictures) (Zhang et al., 2016), and Non-verbal ToM Test (NTT, to make inferences regarding characters' intentions from pictures) (Yeh et al., 2015). The descriptions of these tasks are summarized in Supplementary Table 1.

2.5.2. Verbal ToM and visual ToM

All tasks were verbal to some extent, as they involved verbal instructions and responses (Henry et al., 2013). However, tasks were coded as visual or verbal depending on the mode of actual presentation (Bora and Berk, 2016). Verbal ToM can be evaluated through several tasks such as the FPT, FBT-1, FBT-2, HT, SST, VSIT, ASC, and TASIT. Similarly, visual ToM can be assessed through various tasks such as the RMET, CT, CPT, CIT, MST, IDT, and NTT. The classification of these tasks was based on the methodological similarity as judged by the authors.

Table 1
Characteristics of studies investigating ToM in TBI.

Study	Sample (female)		Age (SD)		GSC score	ToM task
	TBI	HC	TBI	HC		
Bivona et al., 2015	20 (4)	20 (3)	36.9 (16.01)	36.7 (15.4)	≤ 8	FPT
Bivona et al., 2014	28 (7)	28 (7)	NA	34.5 (9.9)	≤ 8	FBT-1, FPT
Bosco et al., 2018	35 (6)	35 (6)	37.51 (12.25)	37.26 (11.58)	4.8 (1.97)	FBT-1, SST
Byom and Turkstra, 2017	21(6)	23 (11)	33	28	≤ 12	VSIT
Cutica et al., 2014	20 (3)	20 (5)	34.7 (7.94)	33	5.6 (3.2)	FBT
Dal Monte et al., 2014	109 (0)	29 (0)	63.3 (0.3)	63.3 (0.7)	NA	RMET
Geraci and Cantagallo, 2011	18	20 (6)	36.1 (10.9)	36 (9.27)	6.9 (3.95)	SST, FBT-2
Geraci et al., 2010	18	20 (6)	36.1 (10.9)	36 (9.27)	6.9 (3.95)	RMET, FPT
Havet-Thomassin et al., 2006	17 (2)	17(2)	35.2 (12.2)	35.4 (13.7)	5 (1.5)	RMET, CIT
Henry et al., 2006	16 (2)	17	44.4 (13.36)	NA	11.3 (3.51)	RMET
Honan et al., 2015	25 (7)	25 (7)	47.52 (12.09)	48.52(12.98)	NA	TASIT Part 2, TASIT Part 3, RMET
Hynes et al., 2011	16 (1)	16 (2)	39.9 (12.2)	35.5 (12)	6.2 (2.8)	ASC
Kelly et al., 2014	26 (7)	24 (7)	45.62 (14.69)	46.52 (13.86)	NA	FPT, HT
Martin and McDonald, 2005	16(4)	16(6)	39.43 (10.72)	34.87 (12.34)	NA	ToM stories
May et al., 2017	40 (12)	32 (7)	40.1 (13.2)	35.2 (13.4)	6.6 (3.9)	FPT, HT, CT, CPT
McDonald et al., 2017	30 (5)	30 (5)	47.27 (14.64)	46.37 (13.52)	NA	TASIT Part 2, TASIT Part 3
McDonald and Flanagan, 2004	34 (9)	34 (12)	41 (12)	36 (13)	NA	TASIT Part 2, TASIT Part 3
Milders et al., 2003	17 (7)	17 (10)	30.5 (13.3)	29.1(12.1)	6.2 (2.6)	RMET, FPT
Muller et al., 2010	15 (2)	15 (2)	37.2 (12.3)	37 (12.5)	4.8 (1.7)	FPT, FBT-1, FBT-1, CIT, RMET
Saint-Jean et al., 2019	15 (5)	25 (11)	32.6 (13.5)	30.4 (12.4)	7.42 (3.68)	FPT
Spikman et al., 2012	28 (8)	33 (16)	30.1 (12.9)	37.9 (13.2)	≤12	FPT, CT
Theadom et al., 2019	121 (58)	121 (54)	40.28 (19.25)	40.24 (19.39)	13–15	TASIT Part 2, TASIT Part 3
Turkstra, 2008	19 (9)	19 (9)	37.2 (15.18)	38.08 (15.19)	NA	RMET, VSIT
Ubukata et al., 2014	20 (6)	28 (14)[1], 20 (10)[2], 30 (14)[3]	36 (12.8)	34.9 (8.1)[1],35 (7.1)[2], 39.1 (10.8)[3]	NA	FPT[1], RMET[2], MST[3]
Westerhof-Evers et al., 2019	63 (12)	72 (23)	42 (13)	45 (15.4)	≤12	CT, FPT
Wilu Wilu et al., 2019	25 (10)	28 (11)	32.21 (11.09)	31.51 (12.82)	5.41 (1.54)	RMET, FBT-1, FBT-2
Yeh et al., 2015	23 (9)	19 (8)	NA	30.58 (12)	11.63 (3.22)	FPT, SST, NTT
Zhang et al., 2016	196(48)	80 (17)	40.92 (11.65)	41.61 (10.28)	NA	FPT, FBT, IDT

TBI = traumatic brain injury; HC = healthy controls; SD = standard deviation; NA = not available; GCS = Glasgow Coma Scale; ToM = theory of mind; FPT = Faux Pas Test; RMET = Reading the Mind in the Eyes Test; FBT = False Belief Test; FBT-1 = First Order False Belief Test; FBT-2 = Second Order False Belief Test; SST = Strange Stories Test; CT = Cartoon Test; CPT = Cartoon Predictions Test; VSIT = Video Social Inference Test; HT = Hinting Test; TASIT = The Awareness of Social Inference Test; MST = Moving-shapes Test; ASC = Assessment of Social Context Task; CIT = Character Intentions Task; IDT = Interpretative Diversity Test; NTT = Non-verbal ToM test.

2.5.3. Cognitive ToM and affective ToM

Cognitive ToM concerns the ability to understand the intentions, beliefs, and thoughts of the self and others, without any personal or emotional involvement. It can be evaluated through several tasks such as the FBT-1, FBT-2, HT, SST, IDT, CPT, CIT, MST, VSIT, ASC, as well as the cognitive subcomponents of the TASIT, CT, FPT, and NTT. Affective ToM implies inferences about the emotional states of others (feelings, emotions) on the basis and the comprehension of our own emotions. It can be evaluated through several tasks such as the RMET and the affective subcomponents of the TASIT, CT, FPT, and NTT. The classification of these tasks was based on the methodological similarity as judged by the authors.

2.6. Statistical analysis

Meta-analyses were conducted with a random-effects model using the Stata 15.0 software package (Masi et al., 2015). The mean effect size (Hedges' g) and 95 % confidence interval (CI) were calculated to estimate differences in ToM performance between adult patients with TBI and HC groups. The magnitude of Hedges' g was interpreted using Cohen's d effect size convention described as 0.20 for small, 0.50 for medium, and 0.80 for large (Cohen, 2013; Hedges, 1981).

As some studies did not provide a total mean score on ToM performance or included more than one individual ToM task, pooled effect sizes were aggregated by computing the mean effect size (and standard error) (Scammacca et al., 2014). Similarly, when studies reported the effect size per subgroup (i.e., by clinical subtypes [moderate-to-severe TBI patients] or by ToM impairments in different aspects [verbal/visual ToM and cognitive/affective ToM]), data were pooled into an overall effect size (Velikonja et al., 2019).

We used I^2 statistics to assess study heterogeneity classifying I^2-values < 50 % as small heterogeneity, 50–75 % as medium heterogeneity, and > 75 % as large heterogeneity (Higgins and Thompson, 2002). To assess the risk of publication bias, inspections of funnel plots and the Egger test were used (Egger et al., 1997). If publication bias was found, the trim-and-fill method was applied, providing effect sizes adjusted for publication bias (Duval and Tweedie, 2000).

To investigate ToM performances, meta-regression analyses were conducted with reference to various factors including gender, age, education level, disease duration, GCS score, and quality assessment score with a random-effects model using the restricted-information maximum likelihood method. The significance level was set at $p < 0.05$.

3. Results

3.1. Study characteristics

The flow chart of the study selection process is shown in Fig. 1. A total of 2962 records were retrieved, 50 of them initially meeting the inclusion criteria. One of these studies was excluded because the samples included adolescents (Allain et al., 2020). Two of these studies were excluded for having a sample size under 10 (Byom and Turkstra, 2012; Stone et al., 1998). Five of these studies did not include an HC group (Gabbatore et al., 2015; McLellan and McKinlay, 2013; Milders et al., 2006, 2008; Prado Guzman et al., 2017). Eight studies were excluded for lack of sufficient data to calculate the effect sizes and standard errors of the ToM measures (Apperly et al., 2007; Balaban et al., 2019; Bara et al., 1997; Bibby and McDonald, 2005; Channon et al., 2005; Leopold et al., 2012; Mintz et al., 1995; Turkstra et al., 2018). Six studies were excluded as their samples overlapped with those of other studies (Bosco et al., 2017; McDonald et al., 2019, 2003; McDonald et al., 2014, 2018; Westerhof-Evers et al., 2017). Eventually, 28 studies consisting of 1031 patients with TBI (mean age = 41.8 years; standard deviation [SD] = 11.9 years; 28.1 % female) and 861 HC (mean age = 39.4 years; SD = 12.8 years; 33.6 % female) were included in the meta-analysis (Table 1). Thirteen of these studies reported GCS scores (Bosco et al., 2018; Cutica et al., 2014; Geraci and Cantagallo, 2011; Geraci et al., 2010; Havet--Thomassin et al., 2006; Henry et al., 2006; Hynes et al., 2011; May et al., 2017; Milders et al., 2003; Muller et al., 2010; Saint-Jean et al., 2019; Wilu Wilu et al., 2019; Yeh et al., 2015). Three of them clearly stated that GCS scores were measured at the hospital arrival (Geraci et al., 2010; Hynes et al., 2011; Wilu Wilu et al., 2019). Others did not report the measurement time of GCS scores, although by default it is usually measured at the hospital arrival. The mean GCS scores across studies ranged from 2 to 15, which suggested that patients included in the current meta-analysis had mild-to-severe disease severity.

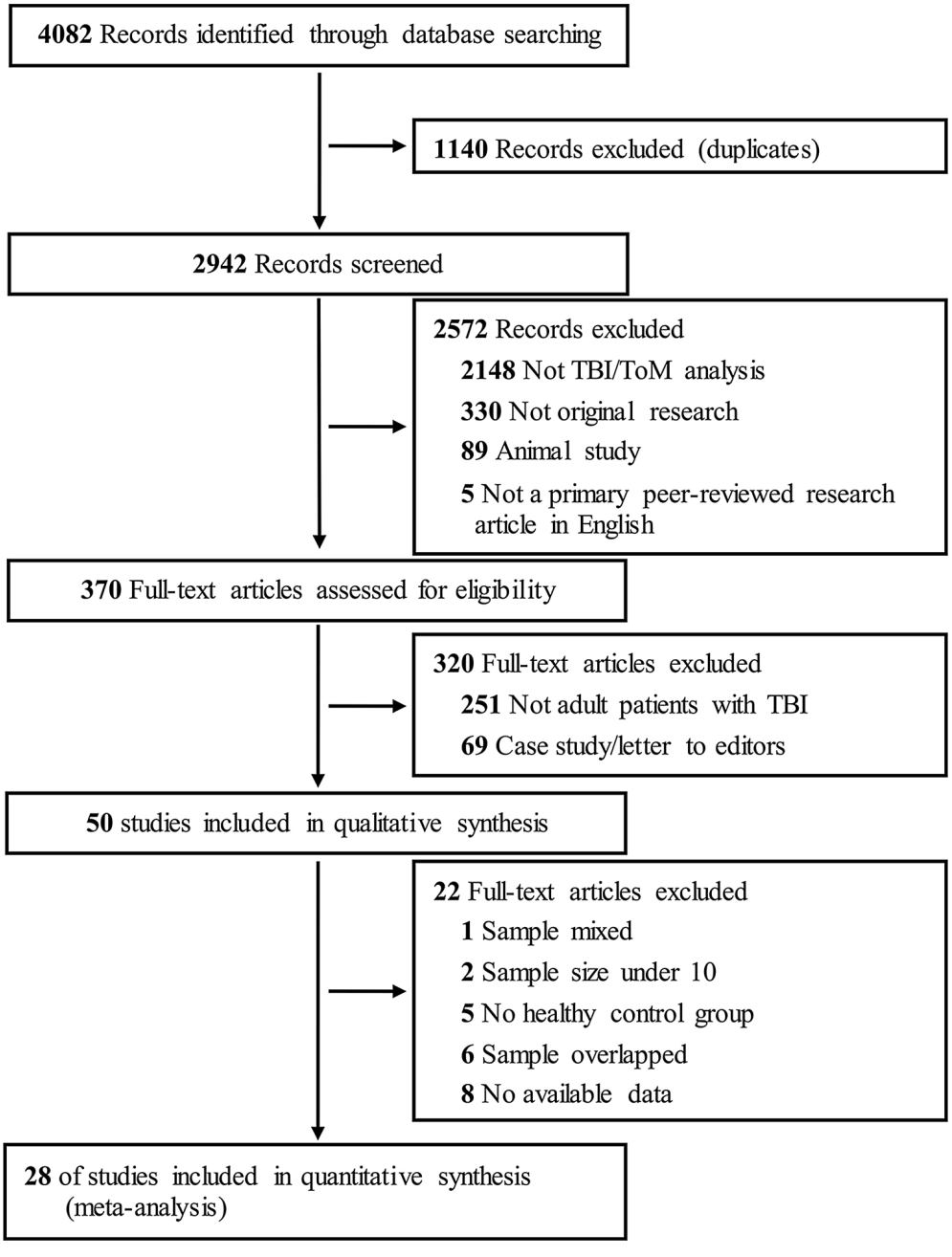

Fig. 1. Flowchart of identification and screening for the eligible studies.
TBI = traumatic brain injury; ToM = theory of mind.

3.2. Study quality assessment

The results of the study quality assessment are shown in Table 2. The mean score was 7.14 (SD = 0.52), and 26 of the 28 case-control studies were awarded ≥ 7 stars and considered of high quality.

3.3. ToM impairment in adults with TBI

ToM differences between adults with TBI and HC are presented in Table 3 and Fig. 2. The meta-analysis showed that adult patients with TBI had significantly worse ToM performance than HC with a large effect size (g = -1.13, 95 % CI [-1.36, -0.89], number of studies [n] = 28, z = -9.34, p < 0.001).

The meta-analysis also revealed that the effect size distribution was significantly heterogeneous, and this heterogeneity was large (I^2 = 86 %), which was further explored to assess the risk of publication bias. The inspection of the funnel plots (Supplementary Fig. 1A) and the statistically significant results of the Egger test (t = -3.14, p = 0.004) indicated the existence of reporting bias. A trim-and-fill analysis resulted in the imputation of one study (Dal Monte et al., 2014), where the sample was limited to older male veterans with focal penetrating TBI and brain injuries were not randomly distributed (i.e., some brain areas were over- and others underrepresented). After exclusion of this study, the effect size for ToM impairment was slightly reduced (g = -0.97, 95 % CI [-1.12, -0.82], n = 27, z = -12.39, p < 0.001), and the distribution of effect sizes indicated medium heterogeneity (I^2 = 64 %). Although the Egger test result was still statistically significant (t = -3.68, p = 0.001), a trim-and-fill analysis did not result in the imputation of any further studies, and the effect size remained the same (Fig. 3).

Table 2
Quality evaluation of included studies.

Study	S1	S2	S3	S4	C	E1	E2	E3	Sum
Bivona et al., 2015	★	★	–	★	★★	★	★	★	8
Bivona et al., 2014	★	★	–	★	★★	★	★	★	8
Bosco et al., 2018	★	–	–	★	★★	★	★	★	7
Byom and Turkstra, 2017	★	–	–	★	★★	★	★	★	7
Cutica et al., 2014	★	–	–	★	★★	★	★	★	7
Dal Monte et al., 2014	★	–	–	★	★★	★	★	★	7
Geraci and Cantagallo, 2011	★	–	–	★	★★	★	★	★	7
Geraci et al., 2010	★	–	–	★	★★	★	★	★	7
Havet-Thomassin et al., 2006	★	–	–	★	★★	★	★	★	7
Henry et al., 2006	★	–	–	★	★★	★	★	★	7
Honan et al., 2015	★	–	★	★	★★	★	★	★	8
Hynes et al., 2011	★	–	–	★	★★	★	★	★	7
Kelly et al., 2014	★	–	–	★	★★	★	★	★	7
Martin and McDonald, 2005	★	–	–	★	★★	★	★	★	7
May et al., 2017	★	–	–	★	★★	★	★	★	7
McDonald et al., 2017	★	–	★	★	★★	★	★	★	8
McDonald and Flanagan, 2004	★	–	★	★	★★	★	★	★	8
Milders et al., 2003	★	–	–	★	★★	★	★	★	7
Muller et al., 2010	★	–	–	★	★★	★	★	★	7
Saint-Jean et al., 2019	★	–	–	★	★★	★	★	★	7
Spikman et al., 2012	★	★	–	★	–★	★	★	★	7
Theadom et al., 2019	★	★	–	★	★–	★	★	★	7
Turkstra, 2008	★	–	–	★	★–	★	★	★	6
Ubukata et al., 2014	★	–	–	★	★–	★	★	★	6
Westerhof-Evers et al., 2019	★	–	–	★	★★	★	★	★	7
Wilu Wilu et al., 2019	★	–	–	★	★★	★	★	★	7
Yeh et al., 2015	★	–	–	★	★★	★	★	★	7
Zhang et al., 2016	★	★	–	★	★★	★	★	★	8

We herein selected "age" as the most important adjusting factor and selected "education level" as other controlled factor. S1: Is the case definition adequate? ; S2: Representativeness of the cases; S3: Selection of Controls; S4: Definition of Controls; C: Comparability of cases and controls on the basis of the design or analysis; E1: Ascertainment of exposure; E2: Same method of ascertainment for cases and controls; E3: Non-Response rate.

3.3.1. ToM in verbal and visual tasks

The differences between adults with TBI and HC regarding verbal ToM and visual ToM are presented in Table 3 and Fig. 4. The meta-analysis revealed that adult patients with TBI performed significantly worse than HC with large effect sizes in verbal ToM (g = -1.00, 95 % CI [-1.22, -0.79], n = 25, z = -9.19, p < 0.001) and visual ToM (g = -1.04, 95 % CI [-1.23,-0.85], n = 14, z = -10.75, p < 0.001).

For visual ToM tasks, the heterogeneity across studies was small (I^2 = 38 %), but there was large heterogeneity for the distribution of effect sizes in verbal ToM tasks (I^2 = 80 %). The funnel plots for visual ToM and verbal ToM are presented in Supplementary Fig. 1B and Supplementary Fig. 1C, respectively. The Egger test was only significant for verbal ToM (t = -2.63, p = 0.015). This indicated the existence of reporting bias, and a trim-and-fill analysis resulted in the imputation of one study (Wilu Wilu et al., 2019). After exclusion of this study, the effect size for verbal ToM impairment was slightly reduced (g = -0.91, 95 % CI [-1.08, -0.74], n = 24, z = -10.75, p < 0.001), and the heterogeneity of effect size distributions was medium (I^2 = 64 %). Although the Egger test result was still significant (t = -3.13, p = 0.005), a further trim-and-fill analysis did not result in additional imputation, and the effect size remained the same (Fig. 5).

3.3.2. ToM in cognitive and affective tasks

The differences between adults with TBI and HC in cognitive ToM and affective ToM are presented in Table 3 and Fig. 6. The meta-analysis demonstrated that adult patients with TBI were significantly worse compared to HC with large effect sizes in cognitive (g = -1.01, 95 % CI [-1.20, -0.81], n = 26, z = -10.39, p < 0.001) and affective (g = -1.24, 95 % CI [-1.55,-0.97], n = 10, z = -7.98, p < 0.001) ToM performance.

The level of heterogeneity across studies was medium for affective ToM (I^2 = 54 %) but for cognitive ToM, the data revealed large heterogeneity for the distribution of effect sizes (I^2 = 78 %). The funnel plots for cognitive and affective ToM are displayed in Supplementary Fig. 1D and Supplementary Fig. 1E, respectively. The Egger test was statistically significant for both cognitive (t = -2.61, p = 0.015) and affective (t = -3.47, p = 0.008) ToM, suggesting the existence of reporting bias. For affective ToM, a trim-and-fill analysis did not result in the imputation of any study, and the effect size remained substantially unchanged. By contrast, the trim-and-fill analysis for cognitive ToM resulted in the imputation of one study (Wilu Wilu et al., 2019). After exclusion of this study, the effect size for cognitive ToM impairment was slightly decreased (g = -0.91, 95 % CI [-1.06, -0.76], n = 25, z = -11.96, p < 0.001), resulting in medium heterogeneity (I^2 = 60 %). Although the Egger test was still statistically significant (t = -3.01, p = 0.006), a trim-and-fill analysis did not result in the imputation of further studies,

Table 3
Mean weighted effect sizes for ToM differences between TBI and healthy controls.

Test	No. of Studies			g	95 % CI		z	p Value	I^2 Statistic, %	Estimated Hedges g (CI) Trim and fill
TBI versus HC		No. in TBI Group	No. in HC Group							
ToM	28	1031	865	−1.13	−1.36	−0.89	−9.34	<0.001	86	change
ToM*	27	922	836	−0.97	−1.12	−0.82	−12.39	<0.001	64	No change
RMET	9	172	178	−1.30	−1.63	−0.98	−7.91	<0.001	49	No change
FPT	13	502	410	−1.01	−1.27	−0.74	−7.47	<0.001	69	No change
Verbal ToM	25	889	800	−1.00	−1.22	−0.79	−9.19	<0.001	80	change
Verbal ToM*	24	864	772	−0.91	−1.08	−0.74	−10.75	<0.001	64	No change
Visual ToM	14	522	424	−1.04	−1.23	−0.85	−10.81	<0.001	38	No change
cognitive ToM	26	906	819	−1.01	−1.20	−0.81	−10.06	<0.001	78	change
cognitive ToM*	25	881	791	−0.91	−1.06	−0.76	−11.96	<0.001	60	No change
affective ToM	10	195	197	−1.24	−1.55	−0.94	−7.98	<0.001	54	No change
moderate to severe TBI versus HC		No. in moderate to severe TBI Group	No. in HC Group							
ToM	17	435	452	−1.03	−1.22	−0.84	−10.42	<0.001	62	No change

TBI = traumatic brain injury; HC = healthy controls; g = Hedges g; ToM = theory of mind; RMET = Reading the Mind in the Eyes Test; FPT = Faux Pas Test; CI = confidence interval; *: the effect size after trim-and-fill analysis.

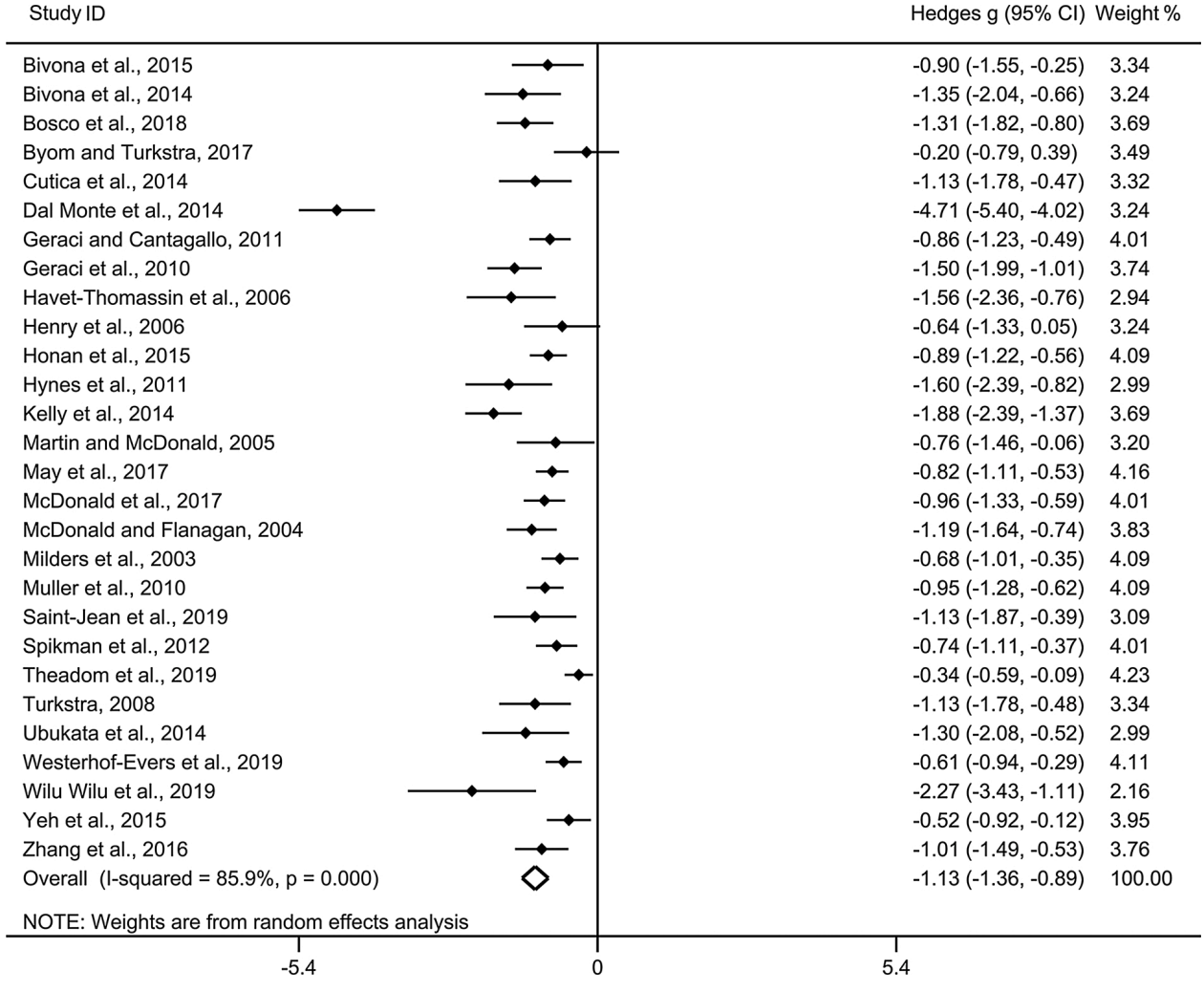

Fig. 2. Forest plots showing effect size estimates (Hedges g) for ToM differences between TBI and healthy controls.
TBI = traumatic brain injury; ToM = theory of mind; CI = confidence interval

and the effect size remained the same.

3.3.3. ToM in individual tasks

The differences between adults with TBI and HC in individual tasks are presented in Table 3 and Figure 8. The meta-analysis showed that adult patients with TBI performed significantly worse than HC with large effect sizes in the RMET (g = -1.30, 95 % CI [-1.63,-0.98], n = 9, z = -7.91, p < 0.001) and FPT (g = -1.01, 95 % CI [-1.27, -0.74], n = 13, z = -7.47, p < 0.001).

The data indicated small and medium heterogeneity across studies

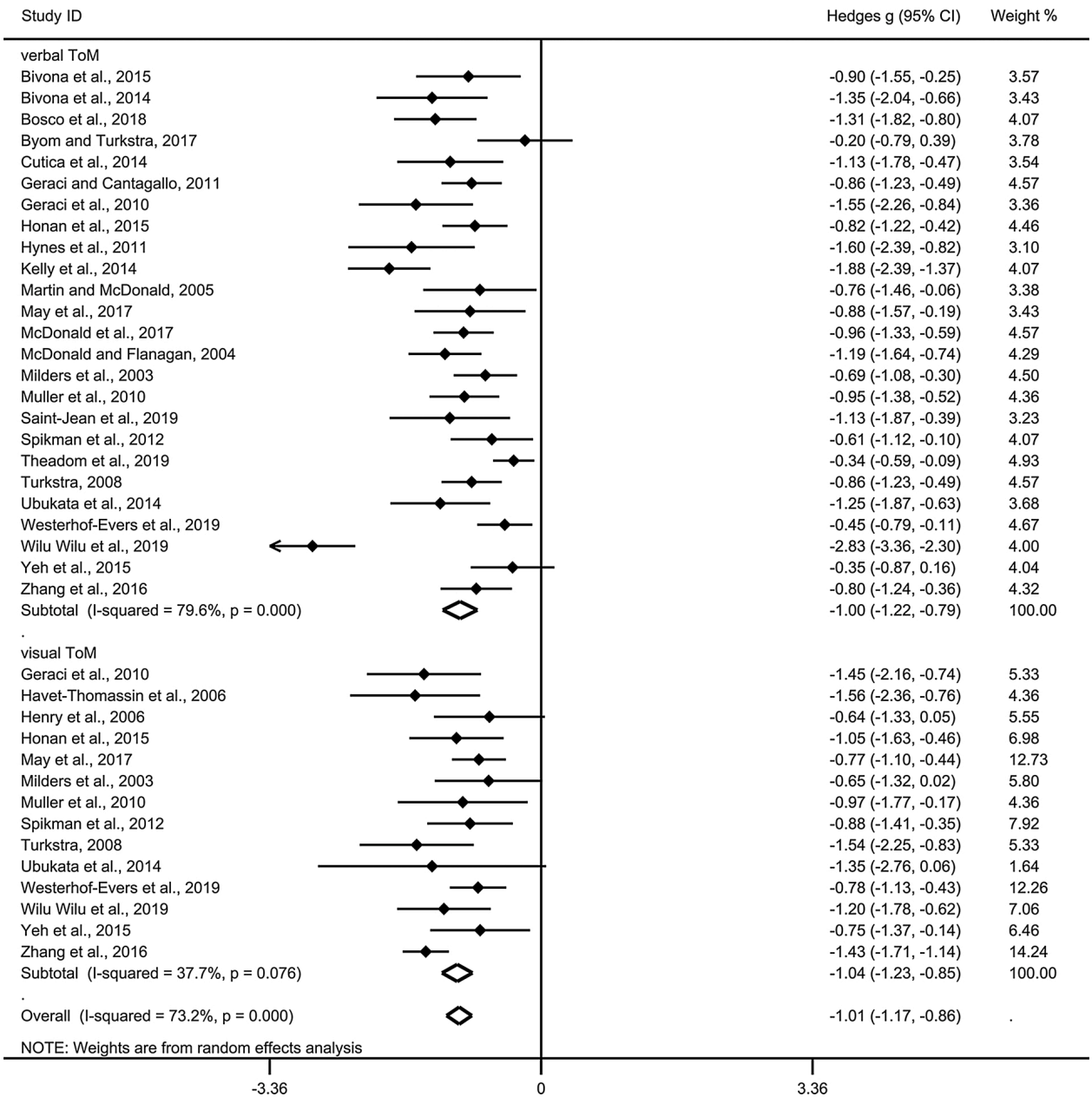

Fig. 3. Forest plots showing effect size estimates (Hedges g) for verbal ToM differences / visual ToM differences between TBI and healthy controls. TBI = traumatic brain injury; ToM = theory of mind; CI = confidence interval

for the RMET (I^2 = 49 %) and FPT (I^2 = 69 %), respectively. The respective funnel plots are displayed in Supplementary Fig. 1F and Supplementary Fig. 1G. Reporting bias according to the Egger test was only observed for the FPT (t = -2.56, p = 0.026). However, a trim-and-fill analysis did not change any of the results.

3.3.4. ToM in adult patients with moderate-to-severe TBI

The ToM differences between patients with moderate-to-severe TBI and HC are presented in Table 3 and Figure 10. The meta-analysis revealed that compared to HC, adult patients with moderate-to-severe TBI had a significantly worse ToM performance with a large effect size (g = -1.03, 95 % CI [-1.22, -0.84], n = 17, z = -10.42, p < 0.001).

The meta-analysis also revealed that the effect size distribution was heterogeneous, and this heterogeneity was of medium size (I^2 = 62 %). The funnel plot in Supplementary Fig. 1H and the statistically significant result of the Egger test (t = -2.46, p = 0.026) suggested the existence of reporting bias. However, a trim-and-fill analysis did not alter any of the results.

The subgroup analysis in patients with mild TBI was not conducted, as only one study was included in meta-analysis.

3.4. Meta-regression analyses

Meta-regression analyses found no significant effect of gender (t = 2.05, p = 0.053, n = 23; Supplementary Fig. 2A), age (t = -0.38, p = 0.708, n = 25; Supplementary Fig. 2B), education level (t = -0.73, p = 0.474, n = 18; Supplementary Fig. 2C), disease duration (t = 0.71, p = 0.491, n = 17; Supplementary Fig. 2D), or the quality assessment score (t = -0.47, p = 0.646, n = 27; Supplementary Fig. 2E) on the severity of ToM impairment in TBI. By contrast, a positive association was noted between ToM deficits and GCS scores in TBI (t = 2.56, p = 0.025, n = 14; Supplementary Fig. 2F).

4. Discussion

To our knowledge, this is the first meta-analysis specifically

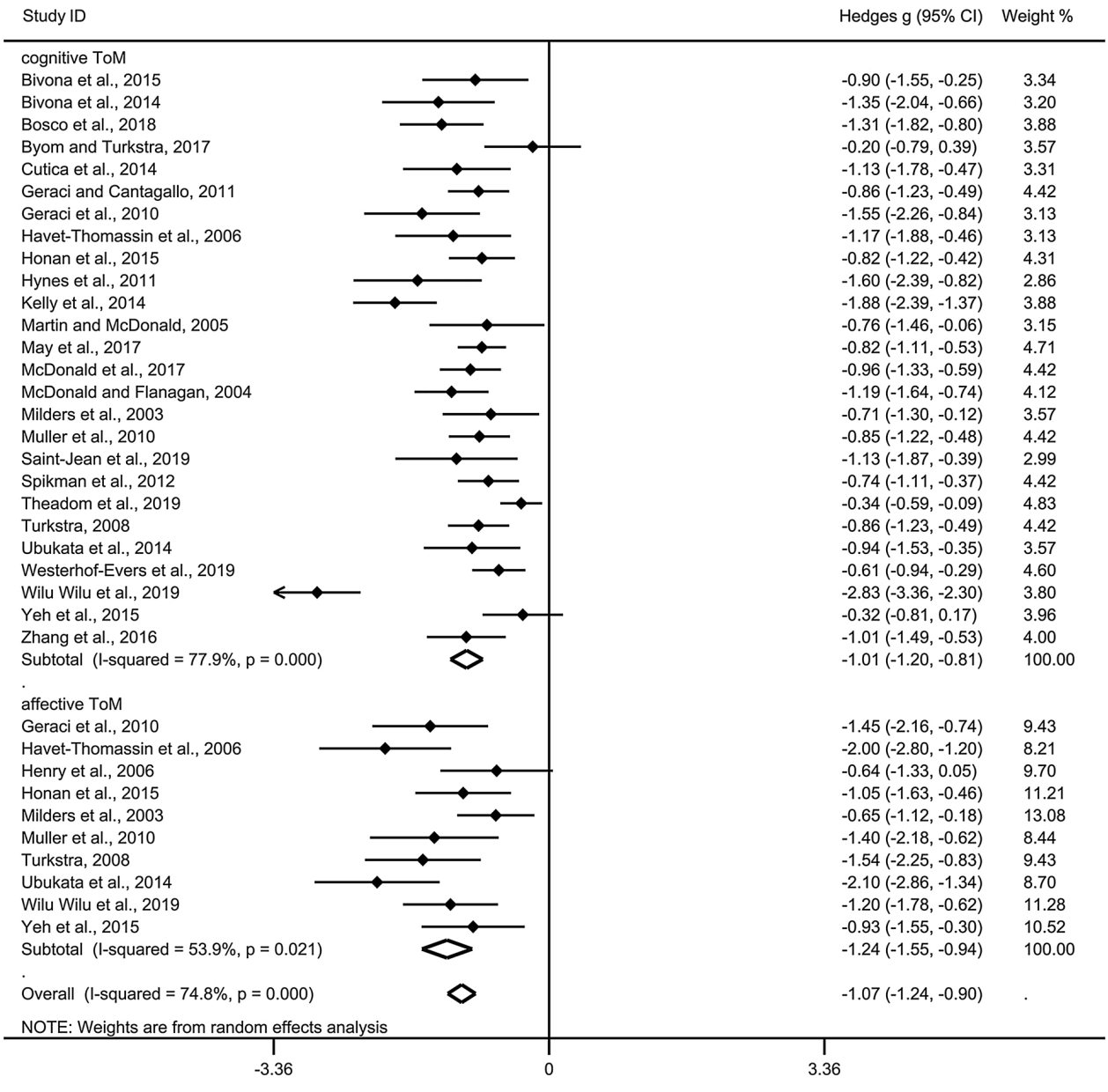

Fig. 4. Forest plots showing effect size estimates (Hedges g) for cognitive ToM differences / affective ToM differences between TBI and healthy controls. TBI = traumatic brain injury; ToM = theory of mind; CI = confidence interval

investigating ToM performance in adults with TBI and comparing impairments in different types of ToM tasks. The current meta-analysis included 28 studies and compared 1031 adult TBI patients with 861 HC. Relative to HC, adult patients with TBI showed significant impairment in ToM (g = -1.13). When investigating the subcomponents of ToM, our results revealed that the impairment in verbal ToM (g = -1.00) was almost as severe as that in visual ToM (g = -1.04). Besides, the meta-analyses demonstrated that ToM deficits were evident in both cognitive ToM (g = -0.91) and affective ToM (g = -1.24) indicating severer impairments in affective ToM. In individual ToM tasks, the RMET had the largest effect size (g = -1.30). Furthermore, our findings showed that ToM impairment was significantly correlated with disease severity.

The effect size of ToM dysfunction suggested that in comparison to HC, adults with TBI exhibited significant difficulties in ToM tasks. The quantitative findings support the conclusions of previous studies that ToM impairment is a common consequence of ABI (including TBI) (Maggio et al., 2020). In addition, our results indicated that adult TBI patients with lower GCS scores may have relatively more ToM impairment. These findings are in line with the results of previous studies that severer TBI predicts poorer ToM performance, indicating that the GCS score is a good predictor for long-term ToM prognosis in TBI (Deighton et al., 2019; Zhang et al., 2016). Our results contribute to prognosis prediction and clinical rehabilitation of ToM in individuals with TBI, but this may warrant further investigation.

Regarding the stimulus mode, our results showed that ToM tasks classified as verbal types revealed significantly impaired ToM performances in TBI. This may be because TBI is associated with communicative-pragmatic impairment (Angeleri et al., 2008; Bara et al., 1997; Bosco et al., 2015, 2017; Cummings, 2017; Fleming et al., 2016; Johnson and Turkstra, 2012) and many ToM tasks rely on linguistic information processing (Fazaeli et al., 2018). In addition, evidence suggests that linguistic and communication difficulties are associated with ToM impairment in TBI (Bosco et al., 2017; Premack and Woodruff, 1978; Wilu Wilu et al., 2019), and deterioration in language proficiency may partially explain the ToM impairment in TBI (Muller et al., 2010). These findings are important as they contribute to the understanding of communicative-pragmatic difficulty in TBI. Moreover, the magnitude of visual ToM deficit was also almost as severe as that of verbal ToM

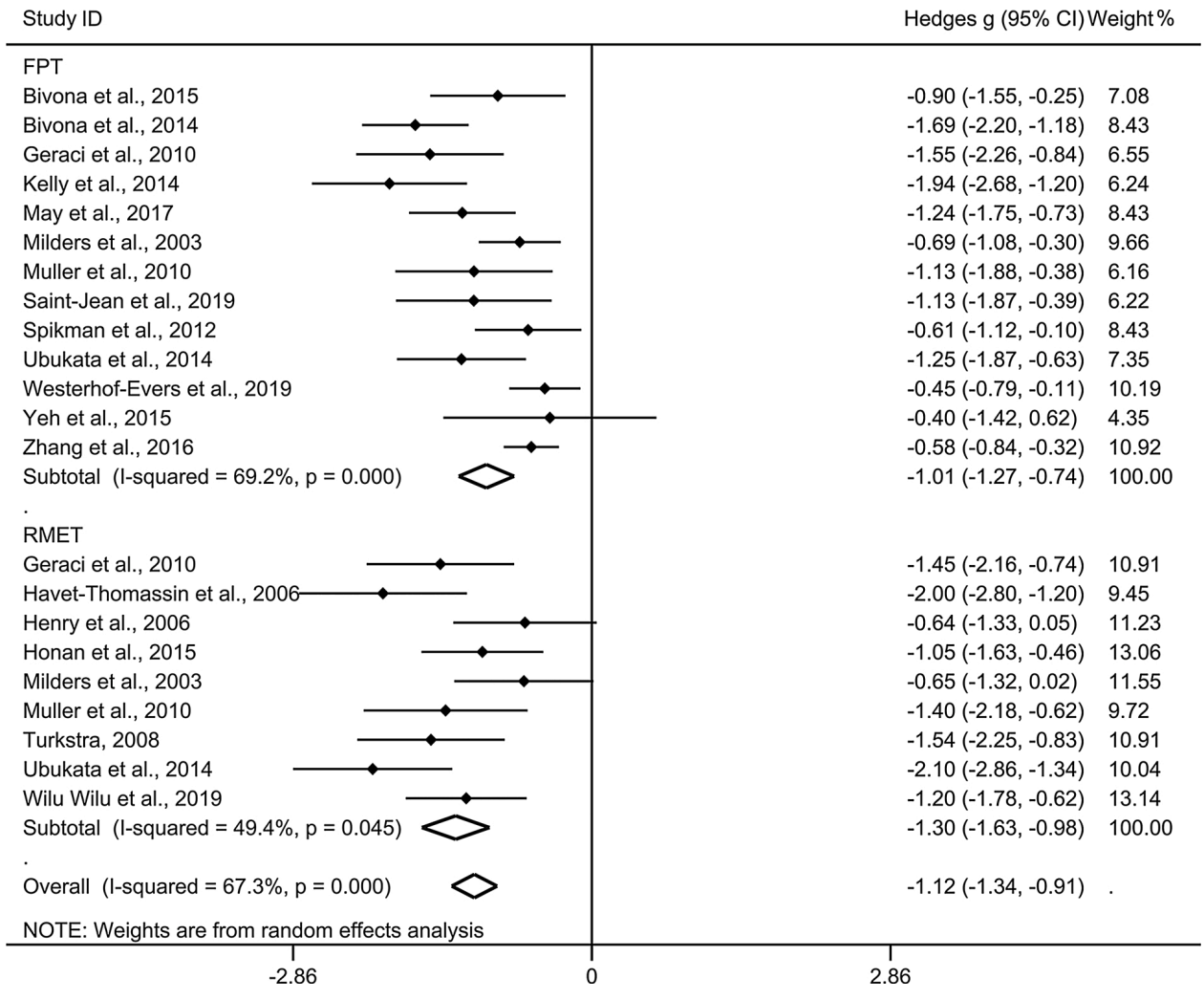

Fig. 5. Forest plots showing effect size estimates (Hedges g) for ToM differences in individual tasks between TBI and healthy controls.
TBI = traumatic brain injury; ToM = theory of mind; CI = confidence interval; FPT = Faux Pas Test; RMET = Reading the Mind in the Eyes Test.

impairment. Considering that the visual pathways and vision-related brain regions related to visuospatial functioning are especially vulnerable in TBI (Brahm et al., 2009; Halterman et al., 2006), and that a large number of ToM tasks rely on visual-processing, visuospatial deficits may also be associated with ToM impairment in TBI (May et al., 2017). However, further research is needed before firm conclusions can be drawn.

Differences in ToM deficits were not only due to disparities in the stimulus mode but were also evident for different stimulus contents. Our results showed that ToM deficits were observed in both cognitive and affective tasks but were more severe in affective ToM. This finding is consistent with a recent suggestion that cognitive and affective ToM domains are dissociated (Kalbe et al., 2007). Specifically, whereas cognitive ToM primarily involves the dorsolateral prefrontal cortex, affective ToM mainly involves the ventromedial prefrontal cortex (Coundouris et al., 2020; Fujiwara et al., 2008; Kalbe et al., 2010; Shamay-Tsoory et al., 2007; Völlm et al., 2006). These areas, especially ventromedial areas, are often injured in TBI, duo to diffuse axonal injury or focal cortical contusion (Bigler, 2007; Fork et al., 2005; Fujiwara et al., 2008; Levine et al., 2008; McDonald et al., 2017; Spikman et al., 2012; Wallesch et al., 2001). Further support comes from the viewpoint that ToM impairments in TBI might be selective (Fazaeli et al., 2018). Besides, Cutica et al. (Cutica et al., 2014) found different degrees of impairment in cognitive ToM and affective ToM. These authors pointed out that it is important to analyze the different ToM subcomponents separately.

For individual ToM tasks, the RMET had the largest effect size (g = -1.33). In this test, participants primarily decode subtle facial affective cues, and the RMET is considered as an appropriate task to assess initial, decoding (or discriminative) ToM processes (Kynast and Schroeter, 2018; Thye et al., 2018). Our finding suggests that in detecting ToM impairments in TBI, the RMET may be more sensitive than FPT. This is consistent with a recent suggestion that the RMET is the best predictor of the cognitive aspects of functional TBI outcomes (Ubukata et al., 2014), but further investigations may be required.

It is worth noting that measurement of deficits in ToM is complicated. To measure ToM, different individual ToM tasks present various verbal stories, pictures, or videos and require patients to understand and explain the thoughts/intentions of some of the characters described or depicted (Baron-Cohen et al., 2001; Happe et al., 1999; Happe, 1994; McDonald et al., 2006; Stone et al., 1998). The entire ToM process is complex and multifactorial in nature. In other words, a complex ToM task involves not only a single neuropsychological function, but possibly also other cognitive functions, such as executive function (EF), attention, speed of information processing, or memory (Bibby and McDonald, 2005; Henry et al., 2006). However, the specific relationship between general cognitive function and ToM in TBI has not yet been determined. For example, some studies have found that EF is at least partially related to ToM (Dennis et al., 2009; Henry et al., 2006), but others found no relationship between EF and ToM (Havet-Thomassin et al., 2006; Muller et al., 2010). Considering that general cognitive deficits in speed of information processing, attention, memory, or EF are commonly found in

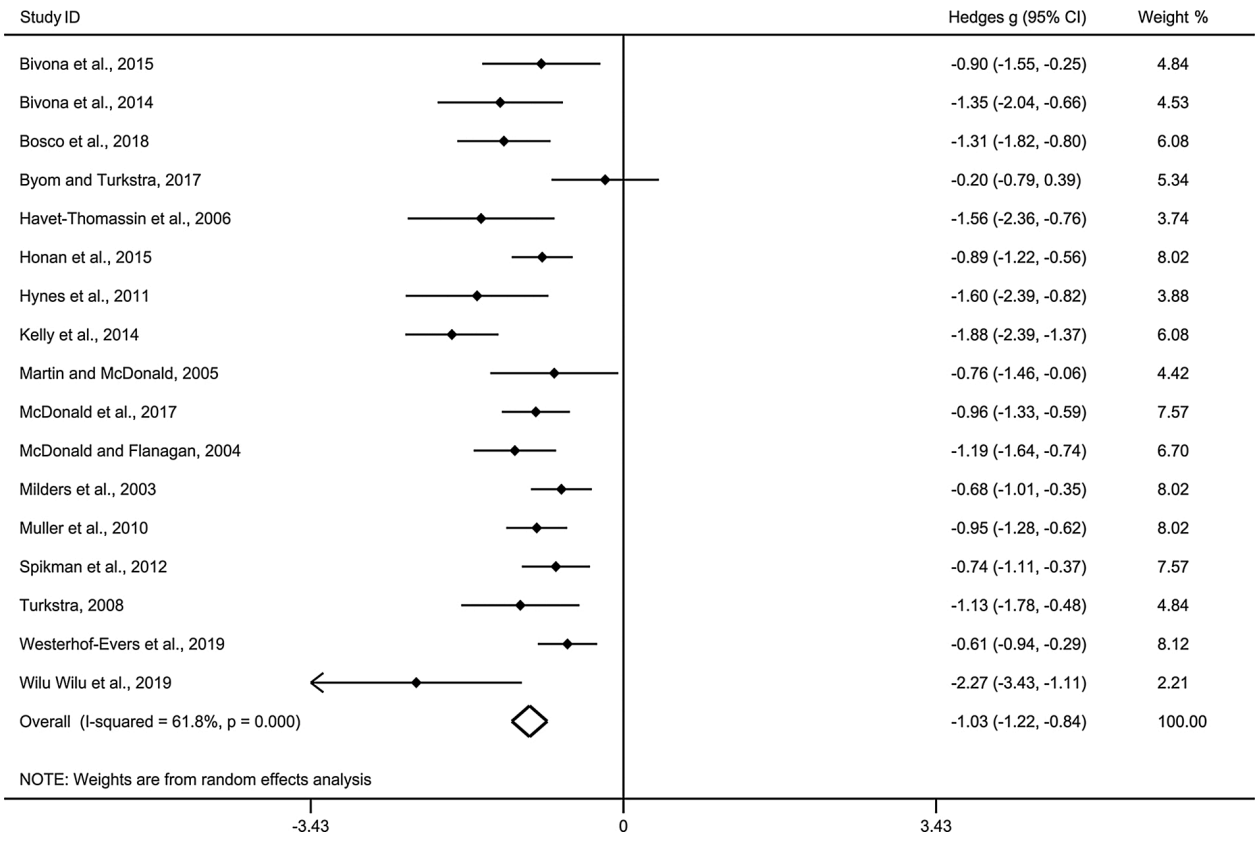

Fig. 6. Forest plots showing effect size estimates (Hedges g) for ToM differences between moderate to severe TBI and healthy controls.
TBI = traumatic brain injury; ToM = theory of mind; CI = confidence interval

TBI (Azouvi et al., 2009; Gorgoraptis et al., 2019; McInnes et al., 2017; Millis et al., 2001), more research is warranted.

Recently, the remediation of impairments in cognitive functioning resulting from TBI has been the focus of attention (Adolphs, 1999, 2001; Forbes and Grafman, 2010; Lieberman, 2007; Semple et al., 2019; Wearne et al., 2020; Zahn et al., 2009). Although an extensive and growing body of literature on the remediation of cognitive dysfunction in TBI exists (Driscoll et al., 2011; Rohling et al., 2009), progress in the development of effective methods for cognitive intervention is quite limited (Driscoll et al., 2011). Current cognitive interventions in TBI are primarily focused on improving nonsocial cognition; only a few treatment studies aimed to improve social cognition after TBI, and most focused only on a single aspect of social cognition (facial affect training, not ToM) (Bornhofen and McDonald, 2008; Guercio et al., 2004; Neumann et al., 2015; Radice-Neumann et al., 2020). In addition, some authors emphasized the potential role of virtual reality (VR) technologies in cognition rehabilitation, which can create an interactive social environment similar to real life without the social cost or pressure encountered in real-life interactions (Burdea, 2003; Calabrò and Naro, 2019; De Luca et al., 2019a, b). Furthermore, evidence suggests that in TBI, the rehabilitation of cognition by VR may lead to better functional outcomes and more appropriate management (Maggio et al., 2019a, b; Maggio et al., 2020). For cognitive interventions of ToM impairments in TBI, ToM performance could be improved by treatment addressing social communication in patients with TBI (Gabbatore et al., 2015). Besides, a multicenter randomized controlled trial showed that ToM is significantly improved in patients with moderate-to-severe TBI following a protocol for multifaceted treatment of social cognition and emotion regulation (T-ScEmo) (Westerhof-Evers et al., 2017). These findings imply that ToM treatments in TBI are promising. Our meta-analysis will help to understand the patterns of ToM function in adult patients with TBI, which may be important for the identification of targets for cognitive interventions and the development of useful training intervention programs.

5. Limitations

There are some limitations to the current meta-analysis. First, the meta-analyses would have benefited from a larger number of studies, as well as from larger sample sizes. Although the overall number of included studies was large in our meta-analysis, the number of available studies for individual ToM tasks was small except for the RMET and FPT. Second, we only included cross-sectional studies, while more longitudinal studies are needed to investigate the ToM performance in adults with TBI. Third, there were some methodological differences, even if the same ToM task was used. For example, some studies assessed the ToM performance using adapted versions or different editions of a task, which could have influenced the outcomes. Fourth, our meta-analyses included only English-language peer-reviewed studies. This may omit published evidence that may exist in other linguistic fields. Fifth, although many clinical factors related to the severity of ToM impairment have been reported, there is still a lack of knowledge regarding other potential confounders such as the impact of drug use. Sixth, the individual tasks for the assessment of ToM require greater sensitivity to assess domain-specific impairments. For example, the RMET, one of the most contested tasks, is hypothesized to be an index of emotion recognition rather than ToM ability (Oakley et al., 2016). Seventh, due to the lack of tasks directly comparing the performance in different ToM aspects (i.e., verbal ToM vs. visual ToM or cognitive ToM vs. affective ToM), we could only conduct indirect comparisons by pooling effect sizes of different individual ToM tasks. In addition, as there is no classification criterion, we could only classify tasks by judging the methodological similarity. Therefore, further studies are required to elucidate potentially ToM-associated features in adults with TBI.

6. Conclusions

The results of this meta-analysis suggest that ToM ability was significantly impaired in adult patients with TBI compared to HC. This impairment is of large magnitude and appears to generalize across different aspects of ToM tasks. Our findings suggest that the performance in ToM tasks may be a good predictor of functional outcomes in adult patients with TBI, which is important for the identification of targets for cognitive interventions and the development of useful training intervention programs. Further studies investigating the neural correlates of ToM deficits in adult patients with TBI and longitudinal studies are needed, which may further reveal the nature and course of ToM impairment in adults with TBI.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgement

We thank Dr. PingLei Pan for his kind suggestions.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.12.010.

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