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Neurocognitive and linguistic correlates of positive and negative formal thought disorder: A meta-analysis

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ABSTRACT

Executive dysfunction and language impairment are the most prominent neuropsychological models of formal thought disorder (FTD) in schizophrenia. However, available studies have provided contradictory findings regarding the accuracy of these models. Furthermore, specific neurocognitive underpinnings of positive FTD (PosFTD) and negative FTD (NegFTD) are not clear. Following the systematic review of schizophrenia studies, a random-effects meta-analysis of the relationship between FTD and neurocognition/language in schizophrenia was conducted in 52 reports including 2805 patients. Neurocognition was significantly associated with both PosFTD ($r = -0.21$, CI = −0.14 to −0.27) and NegFTD ($r = -0.24$, CI = −0.18 to −0.30). Both PosFTD (r = ranged from −0.18 to −0.27) and NegFTD (r = ranged from −0.19 to −0.23) were significantly correlated with verbal memory, visual memory, attention, and processing speed. In meta-analyses of executive functions, PosFTD was significantly associated with working memory ($r = -0.21$), planning ($r = -0.19$), and inhibition ($r = -0.21$) and NegFTD was significantly associated with planning ($r = -0.27$), fluency ($r = -0.27$), and working memory ($r = -0.24$). In meta-analyses of linguistic variables, PosFTD was associated with deficits in syntactic comprehension ($r = -0.27$) and semantic processing ($r = -0.18$). In contrast, NegFTD was associated only with semantic comprehension ($r = -0.21$). Both PosFTD and NegFTD were significantly associated with executive dysfunction, neurocognitive deficits and semantic dysfunction but syntactic deficits were more specific to PosFTD. There were also some distinct patterns of relationships between the pattern of executive dysfunction and types of FTD. Fluency deficit was associated more strongly with NegFTD and poor inhibition was more specifically related to PosFTD. Current findings suggest that neurocognitive and linguistic correlates of PosFTD and NegFTD might be partly different.

1. Introduction

Formal thought disorder (FTD), a hallmark clinical symptom of schizophrenia, refers to deficiencies in organizing thought in a logical sequence in order to attain a certain goal and manifests as disorganized speech resulting from inappropriate use of semantic and other extents of language. As defined by Bleuler, loosening of associations was the main diagnostic indicator of schizophrenia. However, FTD is a complex multidimensional syndrome which includes positive (PosFTD) and negative (NegFTD) formal thought disorder (Roche et al., 2015a, 2015b; Nagels et al., 2016; Kircher et al., 2018). FTD is considered a marker of illness severity (Roche et al., 2015a, 2015b) and a predictor of prognosis in schizophrenia (Andreasen and Grove, 1986; Wilcox et al., 2012). Persisting presence of FTD predicts relapse (Wilcox, 1990; Wilcox et al., 2000); particularly, the presence of FTD at the onset of illness increases rates of relapse in schizophrenia (Liddle and Barnes, 1990). FTD in the prodromal phase is a predictor of conversion to psychosis (Sabb et al., 2010; Wilcox et al., 2014). NegFTD is related to a chronic course of illness (Andreasen and Grove, 1986; Wilcox et al., 2012) with poor response to treatment (Cuesta et al., 1994) and severe PosFTD after the acute phase indicates a poorer prognosis (Harrow and Marengo, 1986).

Neurocognitive correlates of FTD are poorly understood compared to other clinical dimensions of psychotic disorders (i.e. negative symptoms). Neurocognitive impairments in schizophrenia have been extensively documented in the literature. Patients with schizophrenia have deficits in working memory, attention, verbal fluency (Landre and Taylor, 1995; Goldberg et al., 1998; Nestor et al., 1998; Barrera et al., 2005; Stirling et al., 2006; Docherty et al., 2011). Moreover, FTD was shown to be associated with the domains of verbal fluency, semantic processing, executive functioning, attention and working memory (Remberk et al., 2012; Tan and Rossell, 2017). Some evidence suggests that PosFTD and NegFTD might be related to deficits in different neurocognitive domains (Nagels et al., 2016). However, specific neurocognitive underpinnings of PosFTD and NegFTD are not clear yet.

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These results support FTD being a multidimensional construct in which different neurocognitive domains correlate with different FTD extents.

Among neurocognitive domains, executive dysfunction and language impairment might be more specifically associated with FTD. The executive function model emphasizes that impairments in working memory and discourse planning, and attentional deficits are involved in FTD. (Goldberg et al., 1998; Nestor et al., 1998; Barrera et al., 2005; Barrera et al., 2009; Stirling et al., 2006; Docherty et al., 2011; Nagels et al., 2016). In this view, incoherent speech is formed due to either impairment in organizing statements consciously or deficits in retaining focus during speaking (Goldberg et al., 1998). The second model emphasizes semantic processing abnormalities in the emergence of FTD in schizophrenia. Linguistic abnormalities, both in comprehension and production subdomains have been reported in schizophrenia (Condray et al., 1995; Bagner et al., 2003; DeLisi, 2001; Marvel et al., 2004; Perlini et al., 2012; Soriano et al., 2008; Tan et al., 2016). Some evidence suggests that linguistic impairment might be strongly associated with FTD (Goldberg et al., 1998; Barrera et al., 2005; Stirling et al., 2006). Some authors suggested that abnormality in semantic verbal fluency test (and relatively greater impairment of semantic over phonemic fluency) might strongly relate to PosFTD compared to other neurocognitive variables, including executive function (Goldberg et al., 1998). Patients with more severe FTD were suggested to have difficulties in accessing semantic information resulting from the disorganization of the semantic system and deficiency in conceptual knowledge (Goldberg et al., 1998). Syntactic deficits, which are also evident in schizophrenia, might be related to FTD (Bagner et al., 2003; Barrera et al., 2005; Tavano et al., 2008; Moro et al., 2015; Tan et al., 2016).

However, available studies have provided contradictory findings regarding the accuracy of these models of FTD. We aimed to conduct a quantitative systematic review of studies investigating the relationship between FTD and neurocognition, including executive function and language deficits, in schizophrenia. We hypothesized that both PosFTD and NegFTD would be significantly associated with neurocognitive deficits, executive dysfunction, and language deficits.

2. Methods

2.1. Study selection

PRISMA guidelines were used in conducting this meta-analysis (Moher et al. 2009). A literature search was conducted using the databases Pubmed and Scopus to identify the relevant studies (January 1980 to February 2019) using the combination of keywords as follows: ("formal thought disorder" OR "disorganized speech" OR "conceptual disorganization") AND ("cogn*" OR language OR "executive function"). Reference lists of published reports were also searched for additional studies. The literature search was conducted independently by E.B and B·Y and final selection of articles were decided in a joint meeting of all authors. Inclusion criteria for the studies were: (1) Relationship between FTD and cognitive or linguistic functions were investigated in a sample of patients with schizophrenia; (2) FTD was assessed with a standardized clinical instrument including TLC, SAPS/SANS, TDI and others (3) Reported sufficient data to calculate the effect size and standard error for the strength of relationship between FTD and neurocognitive or linguistic impairment. The quality of studies included was assessed using the selection and quality of outcome ascertainment sections of a modified (for cross-sectional studies) version of the Newcastle-Ottawa Scale (Wells et al., 2013). Only one report from studies that share patient samples were included in the meta-analysis unless additional studies report data in additional cognitive domains (Table 1). For these studies, the study with largest sample size for each domain was selected. In this meta-analysis, we did not include studies measuring "communication disturbance" with projective tests or scales such as communication disturbance index (CDI) which measure reference abnormalities, ambiguous word meaning and grammatical unclarity in a speech sample as we were interested in clinical concept of FTD.

Neurocognitive domains included in the current review were verbal memory, visual memory, working memory, processing speed, sustained attention, inhibition, planning/problem solving and verbal fluency (See eTable 1 in the supplement for neurocognitive tests under each domain). Effect size for global neurocognition was calculated by averaging all available neurocognitive domains. Planning/problem solving, fluency, inhibition and working memory domains were considered as measures of executive functions. These neurocognitive domains included 6 MATRICS domains but included additional subdomains to investigate executive dysfunction due to previous hypotheses about executive dysfunction-FTD association. The current meta-analysis also included 3 subdomains investigating semantic (semantic comprehension, naming, semantic-phonemic fluency discrepancy score) and a single domain measuring syntactic (syntactic comprehension) processing. Summary scores for semantic processing and a global linguistic domain were also calculated.

2.2. Statistical analyses

The effect size for neurocognition (and linguistic ability) - FTD correlations (Pearson (r_p) and Spearman's (r_s) r coefficients) for each neurocognitive domain were pooled to calculate a single effect size (r) for each study when more than one cognitive test was available for a neurocognitive domain. Spearman's rho is equivalent to Pearson coefficient applied to ranked data or is slightly smaller if the data are binomial distributed (de Winter et al., 2016; Gilpin, 1993). While conversion of r_s to r_p is possible, there are very slight differences between r_p and r_s coefficients in real life and they are often combined without any conversion in most meta-analyses (de Winter et al., 2016; Gilpin, 1993). However, in addition to using raw r_s values, we also used a converted form of r_p in our meta-analyses in order to check potential impact of using different r measures on outcome of the current meta-analysis (de Winter et al., 2016; Gilpin, 1993). FTD meta-analyses were conducted for PosFTD, NegFTD and GlobalFTD (No differentiation of PosFTD and NegFTD). Cohen gives the following guidelines for interpreting effect sizes in the social sciences: small effect size, $r = 0.1–0.23$; medium, $r = 0.24–0.36$; large, $r = 0.37$ or larger (Cohen, 1992).

Meta-analyses were performed for each neurocognitive and linguistic domain using packages in R environment (Metafor, MAVIS) (Viechtbauer, 2010; Hamilton et al., 2017). Pearson r correlations were analysed after Fisher's Z transformation was applied (Hedges and Olkin, 1985). Same transformation was applied to raw and corrected forms of Spearman's rho. Effect sizes were weighted using the inverse variance method and a random effects model (DerSimonian–Laird estimate) (p-value for significance <0.05). Homogeneity of the distribution of weighted effect sizes was tested with the Q-test and I^2 test. I^2 values of 25%, 50%, and 75%, corresponding to small, moderate, and large heterogeneity. Tau-squared (τ^2), an estimate of between-study variance, was used as a measure of the magnitude of heterogeneity in the random effects model. Selective reporting of positive findings regarding association between neurocognition and FTD might lead to publication bias. Therefore, the possibility of publication bias was assessed by trim and fill method and inspection of the funnel plot of Fisher's *Z*-transformed correlation coefficient and standard error. Egger's test was also used to assess asymmetry of funnel plots when there are at least 5 studies for a meta-analysis of a neurocognitive domain.

After random effects meta-analyses, meta-regression analyses were conducted to investigate the effects of the demographic (age, sex (ratio of males), duration of education), clinical (duration of illness, age of onset) variables on the strength of the associations between global neurocognition and PosFTD and NegFTD. These meta-regression analyses performed with a random-effects model were conducted using the restricted-information maximum likelihood method with a significance level set at $p < 0.05$. Subgroup analyses (acute vs non-acute) were also

Table 1
Characteristics of the studies involved in the current meta-analysis.

Study	Sample	Thought disorder measure	TD dimensions	Age	Cognitive measures	Outcome
Abraham et al., 2007	28 Sch	SAPS, SANS	PosFTD, NegFTD	43.1	Digits backwards, Brixton, Hayling, Stroop	PosFTD is significantly correlated with inhibition deficit
Addington et al., 1991	38 Sch	SAPS	PosFTD	30.9	Fluency, WMS, WCST IQ, visual memory	No relationship
Amaresha et al., 2014	66 Sch	SANS SAPS	NegFTD PosFTD	29.7	Digit symbol	Significantly correlated with impaired digit symbol performance
Bagner et al., 2003	27 Sch	PANSS	PosFTD	38.8	Language comprehension Reading span	Not related
Barrera et al., 2005	31 Sch	CASH positive global	PosFTD	44.0	IQ, Hayling, Brixton, six elements Cognitive estimates Semantic and category fluency Semantic comprehension Syntax comprehension Associative semantics	Related to executive dysfunction and associative semantics
Becker et al., 2012	45 Sch	SANS	NegFTD	44.1	Working memory, attention	NegFTD is related to cognitive impairment
Berenbaum et al., 2008	47 Sch	TLC	PosFTD NegFTD	40.3	Digit span, logical memory, face recognition, verbal fluency, naming	PosFTD is related to WM, memory, naming deficits. NegFTD is related to fluency impairment
Bowie et al., 2004	392 Sch	TLC	NegFTD Global FTD	72.3	Fluency, naming, verbal memory	NegFTD is significantly associated with language and cognitive deficits
Bhattacharyya et al., 2013	47 Sch	PANSS	PosFTD	35.7	TMT, digit symbol, list learning, Verbal fluency, LNS, spatial span, Mazes, visual memory, Digit cancellation	No relationship
Condray et al., 1995	15 Sch	SANS, BPRS	PosFTD NegFTD	36.2	Syntactic comprehension	No relationship
Docherty and Gordinier, 1999	55 Sch	SAPS	PosFTD	33.0	Digit span	Related
Docherty, 2005	47 sch	SAPS	PosFTD	43.0	CPT, TMT A, TMT B, conceptual sequencing	No relationship
Docherty 2012	60 Sch	TLC	PosFTD Global FTD	42.0	CPT, Digit span, WCST, TMT	No relationship
Docherty et al., 2011	34 Sch	TLC	PosFTD NegFTD		Semantic-phonetic fluency	Not related
Dwyer et al., 2014	32 Sch	TLC	PosFTD	39.5	Digit span, LNS, IQ	No relationship
Franke et al., 1992	73 Sch	SAPS SANS	PosFTD NegFTD	32,5	WCST	NegFTD is related
Galaverna et al. 2014a and 2014b	48 Sch	SAPS SANS	PosFTD NegFTD	48,5	IQ, WM, processing speed Fluency	Both NegFTD and PosFTD related
Glahn et al., 2000	62 Sch	SAPS SANS	PosFTD NegFTD	29.6	WCST, AIM	Both NegFTD and PosFTD related
Goldberg et al., 1998	23 Sch	TLC	PosFTD NegFTD	35.0	Semantic comprehension Semantic-phonetic fluency Naming WCST, attention, LNS	TD is associated with language deficits and executive dysfunction
Harvey and Pedley, 1989	36 Sch	TLC	PosFTD NegFTD	30.7	Digit span (with and without distraction)	PosFTD is related attention deficit
Joyce et al., 1996	50 Sch	SANS	NegFTD	36.3	Verbal fluency, Stroop, Boston naming	NegFTD is associated with fluency deficits
Landre and Taylor, 1995	37 Sch	SAPS	PosFTD	47.7	CPT, IQ	Attention is not Related to PosFTD
Langdon et al., 2002	25 Sch	SAPS/SANS	PosFTD NegFTD	31.4	ToL, digit span	NegFTD is related to executive dysfunction
Maeda et al., 2007	79 Sch	TDI	PosFTD	32.3	WCST, WMS,	No relationship
Merrill et al., 2017	51 Sch	Alogia	NegFTD	40.2	Attention, working memory, Processing speed	NegFTD related to Attention/speed impairment
Minor et al., 2015	67 Sch	PANSS	PosFTD	50.5	Composite neurocognition	PosFTD is significantly related to neurocognitive deficits
Moro et al., 2015	58 Sch	TLI	Global FTD	34.7	Syntactic and semantic comprehension	TD related to syntactic impairment
Muralidharan et al., 2018	245 Sch	TLC	PosFTD NegFTD	56.0	Composite neurocognition	NegFTD is related to cognitive impairment
Nagels et al., 2016	51 Sch	TALD	PosFTDNegFTD	35.8	TMT, verbal fluency, digit span,	Different aspects of cognition is associated with PosFTD and NegFTD
Nelson et al., 1998	15 Sch	SAPS	PosFTD	34.0	CPT	PosFTD is associated with attention deficit
Nestor et al., 1998	15 Sch	TDI	PosFTD	37.6	WCST, logical memory, verbal Paired associates, TMT, visual Memory, recurring digits, Alternating semantic categories	Strongly related
Nuechterlein et al., 1986	40 Sch	TDI	PosFTD	22.3	CPT	Not related
Olivier et al., 2017	42 Sch	PTI	PosFTD	24.0	MATRICS	No relationship
Owashi et al., 2009	27 Sch	Harrow's scale	PosFTD	41.5	IQ, WCST	No relationship
Pandurangi et al., 1994	41 Sch	TLC	PosFTD	30.0	CPT	Attention impairment is associated with PosFTD
Ragland et al., 1996	30 Sch	SAPS/SANS	PosFTD NegFTD	31.0	WCST, visual memory	No relationship

Table 1 (*continued*)

Study	Sample	Thought disorder measure	TD dimensions	Age	Cognitive measures	Outcome
Remberk et al., 2012	32 Sch	TLC	Global FTD	16.7	Digit span, verbal fluency	PosFTD is related to fluency deficit
Rodriguez-Ferrera et al., 2001	40 Sch	TLC (posFTD)	PosFTD	42.5	Naming, semantic association, Syntax comprehension, IQ,	Related to semantic Association impairment and Comprehension of syntax
Salavera et al., 2013	102 Sch	TLC	Global FTD	40.8	IQ	No relationship with General intellectual ability
Serper, 1993	20 Sch	TLC	PosFTD NegFTD	30.3	Attention	Related in high demand condition
Stirling et al., 2006	30 Sch	TLC	Global FTD	34.3	Stroop, TMT, digit span, ToL, Fluency, semantic association, Naming, comprehension	FTD is correlated with executive dysfunction and language deficits
Stolar et al., 1994	27 Sch	SANS	NegFTD	36.0	Fluency, semantic comprehension	Fluency impairment is related to NegFTD
Strauss et al., 1993	50 Sch	TLC	Global FTD	34.0	CPT, IQ	Attention deficit is correlated with PosFTD
Stratta et al., 2000	20 Sch	SANS SAPS	PosFTD NegFTD	31,1	WCST, CPT	Attention deficit is correlated with PosFTD
Subotnik et al., 2006	47 Sch	BIT	PosFTD	28.6	List learning, CPT, digit span	PosFTD is related to cognitive deficits
Sumiyoshi et al., 2005	38 Sch	SANS	NegFTD	30.3	Verbal fluency, vocabulary	NegFTD is related to Category fluency deficit
Tamlyn et al., 1992	60 Sch	CASH, SANS	PosFTD NegFTD	44.4	Visual memory	Both aspects of FTD correlated
Tan and Rossell 2017 and 2019	59 Sch	TLC	PosFTD NegFTD Global FTD	44.5	MATRICS, Stroop Syntactic and semantic comprehension	
Van der Does et al., 1993	60 Sch	BPRS	PosFTD	21.2	WCST	EF deficit related

Sch = schizophrenia spectrum, FTD = thought disorder, PosFTD = Positive FTD, NegFTD = Negative FD, SANS = The Scale for the Assessment of Negative Symptoms, SAPS = The Scale for the Assessment of Positive Symptoms, WMS=Wechsler memory scale, WCST = Wisconsin card sorting test, CASH=Comprehensive Assessment of Symptoms and History, PANSS= Positive and Negative Syndrome Scale, TLC=Scale for the Thought, Language and Communication, TMT = Trail making test, BPRS=Brief psychiatric rating scale, EF = executive function, CPT = Continuous performance test, BIT = Bizarre-Idiosyncratic Thinking, ToL = Tower of London test, TLI = thought language index, TDI = Thought disorder index, LNS = Letter number sequencing, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia.

conducted to compare the strength of correlation between global neurocognition and FTD in acute and non-acute samples.

3. Results

The selection process is summarized in eFig. 1. A total of 50 studies (52 reports) including 2805 (65.6% males, mean age = 43.3 years) patients with schizophrenia or schizoaffective disorder were included in the meta-analysis (Table 1).

In meta-analyses of global neurocognition, the distribution of effect sizes was homogeneous for all variables (Table 2). There was a significant correlation between global neurocognition and FTD ($r = -0.22$, $CI = -0.17$ to -0.26, $k = 47$) (Table 2). Global neurocognitive impairment was also associated with both PosFTD ($r = -0.21$, $CI = -0.14$ to -0.27, $k = 36$) (Fig. 1) and NegFTD ($r = -0.24$, $CI = -0.18$ to -0.30, $k = 22$) (Fig. 2). These effect sizes were identical when we used corrected r_s rather than raw r_s in these meta-analyses and therefore we are only reporting meta-analyses with uncorrected r_s in subsequent analyses. The distributions of effect sizes were homogeneous for global neurocognition (Table 2). There was no evidence of publication bias for global neurocognition-FTD relationship ($p = 0.16$).

3.1. Executive functions

Global FTD was significantly associated with poor performance in all executive function domains (r = ranged from −0.17 to −0.22). PosFTD was significantly correlated with working memory ($r = -21$, CI = −0.13 to −0.29, $k = 15$), planning ($r = -0.19$, CI = −0.05 to −0.31, $k = 17$), inhibition ($r = -21$, CI = −0.07 to −0.35, $k = 6$) but not with verbal fluency. NegFTD was significantly associated with poor performance in planning ($r = -0.30$, CI = −0.21 to −0.39, $k = 8$), verbal fluency ($r = -0.27$, CI = −0.20 to −0.34, $k = 8$), working memory ($r = -0.24$, CI = −0.08 to −0.38, $k = 10$) but not inhibition. There was a significant but modest heterogeneity (Table 2) in the distribution of effect sizes for the association between planning and PosFTD ($Q = 50.1$, $p < 0.001$, $I^2 = 68\%$). Similarly, significant but modest heterogeneity was observed for the relationship between working memory and NegFTD ($Q = 25.5$, $p = 0.002$, $I^2 = 65\%$). The distributions of effect sizes were homogeneous for the other variables (Table 2). The funnel plot and Egger's test found evidence of publication bias for inhibition (eFig. 2; Table 2). The strength of correlations between GlobalFTD and inhibition was reduced with trim and fill method ($r = -0.12$, $CI = -0.01$ to -0.22).

3.2. Overall linguistic performance

Global FTD ($r = -0.14$, $CI = -0.08$ to -0.21, $k = 15$), PosFTD ($r = -0.20$, $CI = -0.11$ to -0.29, $k = 12$) and NegFTD ($r = -0.20$, $CI = -0.13$ to -0.28, $k = 8$) were all significantly correlated (Table 3) with summed linguistic impairment (syntactic and semantic) (Fig. 3).

3.3. Semantic processing

Global FTD ($r = -0.14$, $CI = -0.07$ to -0.20, $k = 13$), PosFTD ($r = -0.18$, $CI = -0.08$ to -0.27, $k = 10$) and NegFTD ($r = -0.21$, $CI = -0.14$ to -0.29, $k = 7$) were all significantly correlated with semantic processing deficits (Table 3).

Among subdomains of semantic processing, Global FTD was significantly associated with poor performance in semantic comprehension and naming (r = ranged from −0.18 to −0.23) but not with semantic-phonemic fluency discrepancy score (Table 3). There were also significant correlations between poor performance in naming ($r = -0.22$, $CI = -0.05$ to -0.38, $k = 4$), semantic comprehension ($r = -0.23$, $CI = -0.06$ to -0.38, $k = 4$), and PosFTD. The correlation between semantic-phonemic fluency discrepancy score and PosFTD fell short of significance ($r = -0.16$, $CI = 0.03$ to -0.33). NegFTD was significantly associated with poor performance in semantic comprehension ($r = -0.22$, $CI = -0.02$ to -0.40, $k = 3$) and naming ($r = -0.16$, $CI = -0.01$ to -0.30, $k = 4$), but not with semantic-phonemic fluency discrepancy score. The distributions of effect sizes were homogeneous for all linguistic measures for all FTD variables. In Egger's test and inspection of funnel plots, there was evidence of publication bias for semantic-phonemic fluency discrepancy score (eFig. 3). The strength of correlation between GlobalFTD and semantic-phonemic fluency discrepancy score was reduced with trim and fill method ($r = 0$, $CI = -0.13$ to 0.13).

3.4. Syntactic comprehension

Global FTD was significantly associated with poor performance in syntactic comprehension ($r = -0.27$, $CI = -0.14$ to -0.38, $k = 7$). Syntactic comprehension impairment was significantly associated with PosFTD ($r = -0.27$, $CI = -0.14$ to -0.39, $k = 6$) (Fig. 4) but not with NegFTD.

3.5. Other neurocognitive domains

Global FTD was significantly associated with poor performance in attention ($r = -0.24$, $CI = -0.17$ to -0.31, $k = 18$), processing speed ($r = -0.19$, $CI = -0.08$ to -0.30, $k = 11$), verbal ($r = -0.19$, $CI = -0.10$ to -0.28, $k = 10$) and visual ($r = -0.25$, $CI = -0.14$ to -0.35, $k = 8$) memory. Both PosFTD (r = ranged from -0.18 to -0.27) and NegFTD (r = ranged from -0.19 to -0.23) were also significantly correlated with each of these 4 neurocognitive domains (Table 2). The distributions of effect sizes were homogeneous for all FTD variables for these neurocognitive domains (Table 2). In the inspection of funnel plots and Egger's test, we found no evidence of publication bias for any of these measures (Table 2).

3.6. Meta-regression and subgroup analyses

Meta-regression analyses found no significant effect of age ($Z = -0.04$, $p = 0.97$, $k = 30$), sex ($Z = 0.04$, $p = 0.97$, $k = 27$), duration of education ($Z = -0.23$, $p = 0.81$, $k = 18$), age of onset ($Z = -0.04$, $p = 0.97$, $k = 16$) and duration of illness ($Z = -0.43$, $p = 0.66$, $k = 16$) on strength of correlation between global neurocognition and PosFTD. Similarly, the same variables had no significant impact on the level of correlation between global cognition and NegFTD ($p = 0.50$ to 0.98). In subgroup analyses, there was a significant difference between acute and nonacute samples in strength of correlation between global cognition and PosFTD ($r = -0.12$ vs -0.24, $Q_{bet} = 4.77$, $p = 0.03$), but not between global neurocognition and NegFTD ($r = -0.25$ vs -0.23, $Q_{bet} = 0.05$, $p = 0.83$). In acute state of the illness, PosFTD was not significantly correlated with any neurocognitive domains except attention ($r = -0.24$, $CI = -0.10$ to -0.39, $Z = 3.19$, $p = 0.001$).

There was no significant difference between acute and nonacute samples in strength of correlation between linguistic measures and FTD dimensions.

4. Discussion

The current meta-analysis investigated the neurocognitive and linguistic correlates of FTD in schizophrenia. Our findings suggested that both PosFTD and NegFTD were significantly associated with executive dysfunction, semantic processing abnormalities and neurocognitive deficits but syntactic comprehension deficits were more specific to PosFTD.

Our findings supported the proposed relationship between executive function and FTD. There was evidence for the association between executive functions and FTD for each of 4 domains of executive functions including planning/problem solving, working memory, inhibition and fluency. However, the pattern of relationship between different domains of executive functions and FTD was different for PosFTD and NegFTD. While deficits in both planning and working memory were significantly associated with both aspects of FTD, inhibition was significantly associated with PosFTD. In contrast, NegFTD was significantly associated with fluency but not inhibition deficits. These findings might suggest that the relationship between executive dysfunction and PosFTD might be moderated by difficulties in inhibiting irrelevant material which might lead to planning and working memory impairment. In contrast, difficulties in self-initiation related aspects of executive functions seem to be related to NegFTD. The relationship between executive dysfunction and both aspects of FTD might be related to frontal lobe abnormalities observed in schizophrenia. Consistent with this view, previous studies reported that brain imaging abnormalities in anterior cingulate cortex and orbitofrontal cortex might be associated with PosFTD (Horn et al., 2009; Horn et al., 2010; Sans-Sansa et al., 2013). Also, evidence suggests that fronto-cingular and striatal abnormalities might be related to NegFTD (Palaniyappan et al., 2015; Shaffer et al., 2015).

Table 2
Mean weighted effect sizes for the relationship between formal thought disorder and neurocognition in schizophrenia.

Test	k	Sch	r	95% CI		Z	p	Q-test	Q-test (p)	τ^2	I^2	Bias
Global cognition	47	2657	−0.22	−0.17	−0.26	9.11	<0.001	60.4	0.08	0.01	24	0.16
-PosFTD	36	1813	−0.21	−0.14	−0.27	6.27	<0.001	61.4	0.004	0.02	43	
-NegFTD	22	1573	−0.24	−0.18	−0.30	7.98	<0.001	25.4	0.23	0	17	
Verbal memory	10	864	−0.19	−0.10	−0.28	3.96	<0.001	13.6	0.14	0.01	34	0.22
-PosFTD	8	372	−0.21	−0.07	−0.35	2.95	0.003	12.5	0.09	0.02	44	
-NegFTD	4	596	−0.22	−0.14	−0.29	5.31	<0.001	1.9	0.6	0	0	
Working memory	21	898	−0.22	−0.15	−0.29	5.77	<0.001	24.6	0.22	0.01	19	0.73
-PosFTD	15	615	−0.21	−0.13	−0.29	5.18	<0.001	12.8	0.55	0	0	
-NegFTD	10	488	−0.24	−0.08	−0.38	2.99	0.003	25.5	0.002	0.04	65	
Processing speed	11	576	−0.19	−0.08	−0.30	3.35	<0.001	17.5	0.06	0.02	43	0.12
-PosFTD	7	329	−0.18	−0.06	−0.30	2.81	0.005	8.0	0.24	0.01	25	
-NegFTD	6	350	−0.23	−0.06	−0.38	2.70	0.007	11.4	0.04	0.02	56	
Planning	20	898	−0.22	−0.13	−0.31	4.53	<0.001	36.3	0.01	0.02	47	0.31
-PosFTD	17	762	−0.19	−0.05	−0.31	2.71	0.007	50.1	<0.001	0.05	68	
-NegFTD	8	396	−0.30	−0.21	−0.39	6.19	<0.001	4.1	0.77	0	0	
Inhibition	8	561	−0.19	−0.08	−0.29	3.36	<0.001	7.0	0.43	0	0	0.05
-PosFTD	6	258	−0.21	−0.07	−0.35	2.95	0.003	6.25	0.28	0.01	20	
-NegFTD	4	208	−0.05	0.09	–0.19	0.75	0.46	0.47	0.93	0	0	
Fluency	13	888	−0.17	−0.11	−0.24	5.10	<0.001	8.6	0.74	0	0	0.10
-PosFTD	8	357	−0.08	0.03	–0.18	1.48	0.14	3.9	0.79	0.	0	
-NegFTD	8	703	−0.27	−0.20	−0.34	7.13	<0.001	4.7	0.70	0	0	
Visual memory	8	336	−0.25	−0.14	−0.35	4.44	<0.001	4.3	0.74	0	0	0.02
-PosFTD	8	336	−0.27	−0.16	−0.37	4.76	<0.001	7.3	0.40	0	0	
-NegFTD	4	194	−0.19	−0.05	−0.33	2.63	0.008	2.1	0.55	0	0	
Attention	18	801	−0.24	−0.17	−0.31	6.72	<0.001	17.2	0.44	0	1	0.17
-PosFTD	14	574	−0.25	−0.16	−0.34	5.08	<0.001	17.0	0.20	0.01	23	
-NegFTD	7	344	−0.21	−0.11	−0.31	3.85	<0.001	4.80	0.57	0	0	

r = Effect size of correlation, Bias = p value of the Egger's test, k = number of studies, FTD = Formal thought disorder, PosFTD = Positive FTD, NegFTD = Negative FTD.

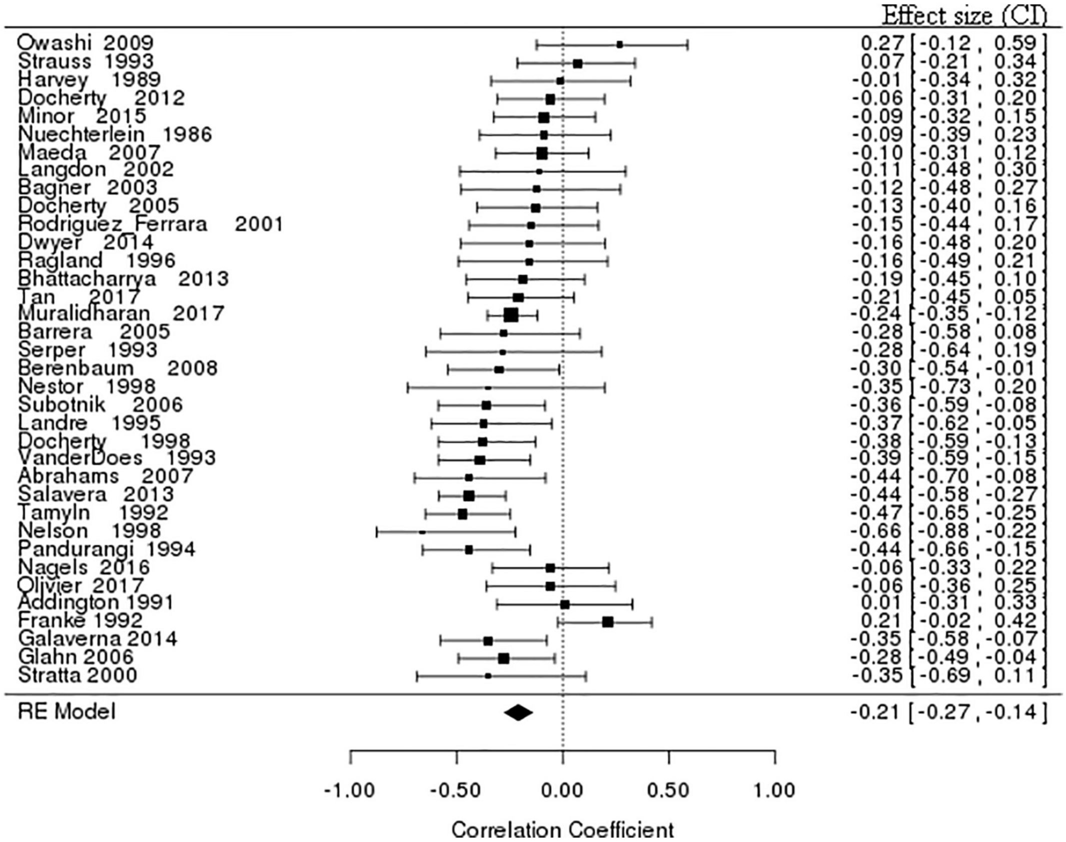

Fig. 1. Forest plot of the meta-analysis of the correlation between PosFTD and global cognition.

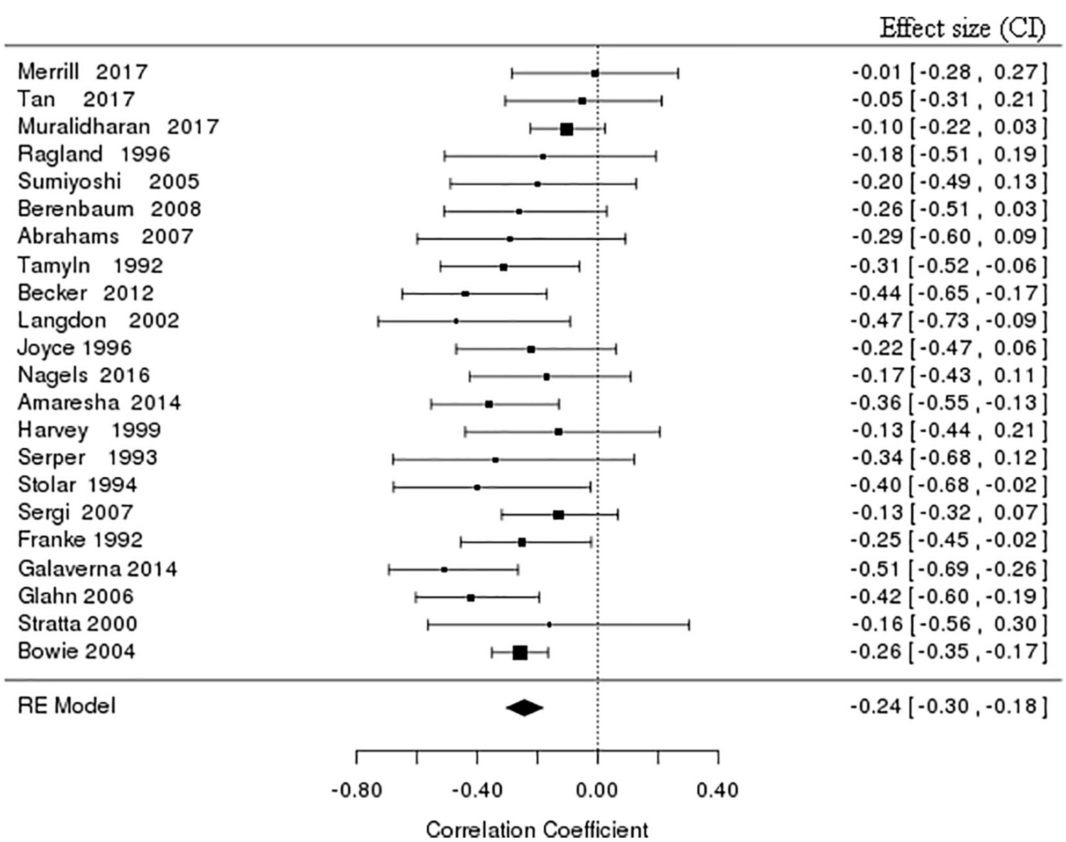

Fig. 2. Forest plot of the meta-analysis of the correlation between NegFTD and global cognition.

Table 3
mean weighted effect sizes for the relationship between formal thought disorder and linguistic variables in schizophrenia.

Test	k	Sch	r	95% CI		Z	p	Q-test	Q-test (p)	τ^2	I^2	Bias
Syntactic/semantic summed	15	941	−0.14	−0.08	−0.21	4.30	<0.001	7.2	0.93	0	0	0.69
-PosFTD	12	492	−0.20	−0.11	−0.29	4.37	<0.001	10.3	0.50	0	0	
-NegFTD	8	642	−0.20	−0.13	−0.28	5.15	<0.001	6.0	0.53	0	0	
Syntactic comprehension	7	258	−0.27	−0.14	−0.38	4.16	<0.001	0.7	0.99	0	0	0.38
-PosFTD	6	228	−0.27	−0.14	−0.39	4.02	<0.001	3.9	0.56	0	0	
-NegFTD	2	72	−0.06	0.19	−0.29	0.45	0.66	0.01	0.95	0	0	
Semantic processing	13	899	−0.14	−0.07	−0.20	4.0	<0.001	6.4	0.90	0	0	0.11
-PosFTD	10	450	−0.18	−0.08	−0.27	3.65	0.003	8.3	0.50	0	0	
-NegFTD	7	627	−0.21	−0.14	−0.29	5.31	<0.001	5.3	0.50	0	0	
Category-letter fluency	5	193	−0.08	0.06	−0.23	1.13	0.26	2.76	0.80	0	0	0.02
-PosFTD	5	193	−0.16	0.03	−0.33	1.61	0.10	6.43	0.17	0.02	38	
-NegFTD	2	57	−0.02	0.25	−0.29	0.16	0.87	0.18	0.68	0	0	
Naming	7	613	−0.23	−0.16	−0.31	5.81	<0.001	4.7	0.58	0	0	0.27
-PosFTD	4	141	−0.22	−0.05	−0.38	2.54	0.01	1.4	0.71	0	0	
-NegFTD	4	512	−0.16	−0.01	−0.30	2.02	0.04	4.2	0.18	0.01	38	
Semantic comprehension	7	276	−0.18	−0.05	−0.30	2.80	0.005	1.8	0.94	0	0	0.73
-PosFTD	4	151	−0.23	−0.06	−0.38	2.65	0.008	2.0	0.58	0	0	
-NegFTD	3	91	−0.22	−0.02	−0.40	2.16	0.03	0.1	0.95	0	0	

r = Effect size of correlation, Bias = p value of the Egger's test, k = number of studies, FTD = Formal thought disorder, PosFTD = Positive FTD, NegFTD = Negative FTD.

Both PosFTD and NegFTD were associated with semantic processing deficits, particularly with semantic comprehension and naming. This finding seemingly supports the proposed relationship between FTD and semantic processing abnormalities. The neurobiological underpinnings of this relationship might be related to abnormalities in the language related regions in schizophrenia. Evidence suggests that PosFTD is associated with structural and functional abnormalities in left superior temporal areas, inferior frontal regions and insula (Wensing et al., 2017; Cavelti et al., 2018; Sumner et al., 2018). NegFTD might be related to abnormalities in middle temporal lobe and insula (Palaniyappan et al., 2015; Winkelbeiner et al., 2018). Interestingly, there was no significant association between semantic-phonemic fluency discrepancy score and FTD. This finding is in contrast with earlier studies (Goldberg et al., 1998). However, it is important to note that our analysis suggested that publication bias played a role in positive findings regarding semantic-phonemic fluency discrepancy score in the earlier literature.

A notable finding in our meta-analysis was the specific relationship between syntactic comprehension impairment and PosFTD. While most of the proposed linguistic models of FTD has emphasized the role of semantic abnormalities, syntactic and higher-order linguistic abnormalities might be more relevant for understanding FTD (Moro et al., 2015). Abnormalities in inferior frontal gyrus and its connections with temporal lobe might be particularly important in deficits of syntactic comprehension (den Ouden et al., 2019).

It is important to note that the relationship between FTD and neurocognitive impairment was not specific to executive functions and linguistic measures. Deficits in global neurocognition and each of the neurocognitive domains explored were significantly correlated with both PosFTD and NegFTD. These findings are not surprising as most of the patient-control differences in neurocognition might be related to between-group differences in global neurocognition (Schaefer et al., 2013). Schizophrenia patients with severe course of illness might present with persistent FTD and global neurocognitive deficit. Therefore, the co-existence of global neurocognitive impairment and FTD can explain the significant relationship between FTD and different cognitive domains. This might be also true for executive dysfunction and linguistic impairment. However, unlike other neurocognitive variables which correlated with both aspects of FTD, NegFTD and PosFTD demonstrated differences in the patterns of relationship between executive dysfunction/linguistic deficits. This finding might suggest that a more specific association between neurocognition, linguistic impairment and different aspects of FTD, beyond moderated by global neurocognitive impairment, might be evident. It is also important to state that the effect sizes for the relationship between FTD and neurocognitive/linguistic impairment indicated small to medium effects. PosFTD had medium-sized associations with syntactic comprehension and visual memory and all other significant correlations indicated a small effect. PosFTD had medium-sized associations with planning, working memory and verbal fluency but all other significant correlations indicated a small effect. These results support FTD being a multidimensional construct in which different neurocognitive, executive function and linguistic domains correlate with different aspects of FTD.

Another interesting finding was the effect of state of the illness on the relationship between PosFTD and neurocognition. In general, PosFTD was significantly correlated with neurocognitive deficits only in the non-acute phase of the illness. This is not surprising as PosFTD, together with delusions and hallucinations, are more pronounced during acute state but PosFTD which persists beyond acute psychotic state is associated with poor prognosis (Roche et al., 2015a, 2015b). Originally, the current study reports a meta-analysis of the relationship between FTD and neurocognition/linguistic abilities. Our findings supported the notion that FTD is associated with deficits in executive functions and linguistic abnormalities. Neurocognitive and linguistic correlates of PosFTD and NegFTD were mostly common but partly different. One may argue that FTD might be simply clinical-level reflection of underlying executive dysfunction and linguistic abnormalities rather than being an independent construct. For example, one could speculate that inhibitory deficits might be related to failure of suppression of irrelevant thought process leading to generation of unconnected thoughts. However, causality between neurocognitive impairment and FTD has not been established yet and observed associations might be confounded with other factors.

Limitations of our current meta-analysis include the cross-sectional nature of our meta-analysis. Another important limitation was the lack of studies investigating neurocognition and FTD in high-risk and first-episode samples. This is particularly important as factors such as medication and co-morbid medical conditions can confound the relationship between FTD and neurocognition. Also, FTD was assessed with different clinical rating scales which might differ in a number of points (i.e., sensitivity, scope of FTD symptoms assessed). Another consideration was the small number of studies available for some neurocognitive variables, including linguistic variables. It is important to note that schizophrenia is characterized with communicative disturbances beyond FTD, neurocognitive correlates of communicative disturbances are needed to be further investigated. Finally, developing objective methods for assessing FTD such as automatic analysis of speech connectedness might be important to reveal neurocognitive underpinnings of these abnormalities in schizophrenia (Palaniyappan et al., 2018).

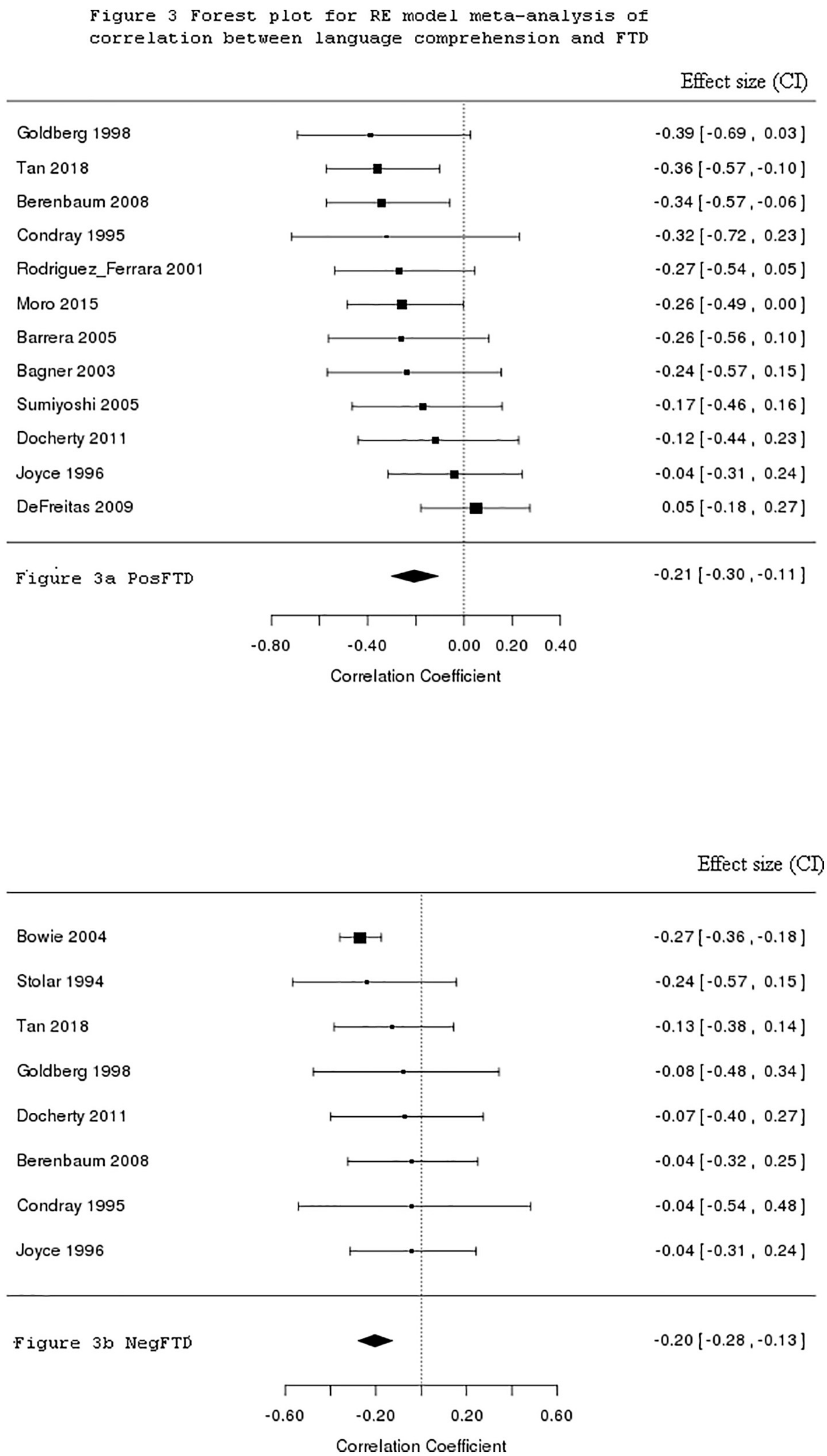

Fig. 3. Forest plot of the meta-analysis of the correlation between PosFTD, NegFTD and linguistic comprehension.

As a conclusion, the current findings suggested that both PosFTD and NegFTD were significantly associated with executive dysfunction, semantic processing abnormalities and neurocognitive deficits but syntactic comprehension deficits were more specific to PosFTD. This finding suggests that neurobiological underpinnings of NegFTD and PosFTD are likely to be distinct. Further longitudinal studies in high-risk and first-episode samples with multiple assessments of FTD, neurocognition and their neuroanatomical correlates using advanced methods (i.e. connectome analyses and automatic speech analyses) are required to understand the complex phenomenon of PosFTD and NegFTD in schizophrenia.

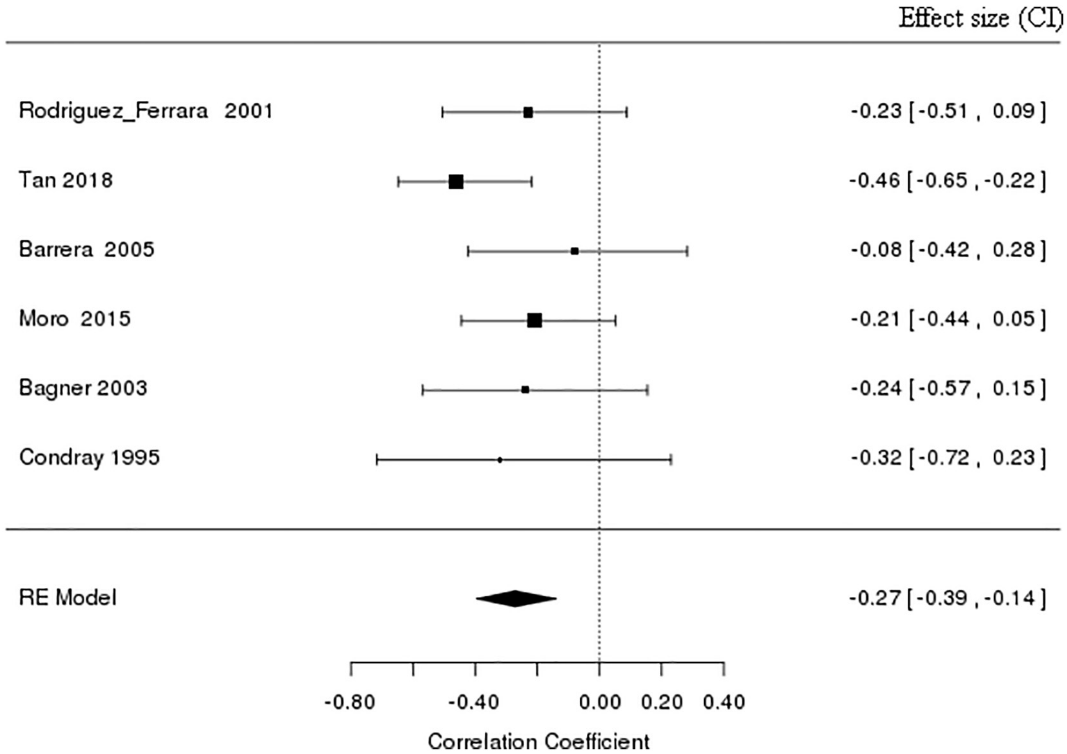

Fig. 4. Forest plot of the meta-analysis of the correlation between PosFTD and syntactic comprehension.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.025.

Contributors

EB and BY conducted the literature search. EB conducted the analyses and wrote the first draft. All authors contributed to the planning of the study. All authors critically reviewed the paper. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

The authors have no conflicts of interest regarding subject of this manuscript.

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Not relevant

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