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Review article

Deficiencies in Theory of Mind in patients with schizophrenia, bipolar disorder, and major depressive disorder: A systematic review of secondary literature

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ABSTRACT

Deficiencies in Theory of Mind (ToM) are consistently found in individuals with schizophrenia (SZ), major depressive disorder (MDD), and bipolar disorder (BD). However, the character of these deficits and their role in the pathogenesis of mental illness remains poorly understood.

This systematic review synthesizes the available secondary literature pertaining to ToM functioning in individuals with MDD, BD, or SZ, and their respective spectrum disorders in order to delineate disorder or symptom specific patterns of ToM impairment.

Literature suggests that ToM deficits increase in severity along the affective-psychotic spectrum, with mild deficits in patients with MDD, and severe deficits in patients with mania or psychosis. Furthermore, ToM deficits appear to be part of a broader developmental phenotype associated with SZ and BD, as suggested by findings of attenuated impairments in ToM in remitted patients with SZ or BD, unaffected first-degree relatives of patients, and clinical high-risk groups.

Future psychiatric research on ToM should aim to disentangle relationships between ToM deficits and specific symptom dimensions transdiagnostically, and employ standardized, construct-specific ToM tasks.

1. Introduction

Humans are social animals. As such, our social skills must be expertly attuned to the mental states of the individuals we interact with daily, as to enable efficient communication and avoid conflict. Accordingly, evidence is growing that deficits in social skills play a role in the pathogenesis of many psychiatric disorders. In psychotic disorders, it has been argued that several core symptoms (reality distortion, negative symptoms and disorganization) exist secondary to the loss of social cognitive functions (Pickup and Frith, 2001). In addition, a causal role for social cognitive dysfunction has been hypothesized in the establishment and maintenance of affective symptoms in mania (Mansell and Pedley, 2008) and depression (Weightman et al., 2014). Furthermore, social isolation and deficits in social cognitive functions have been linked to overall functional outcome across individuals with psychiatric disorders (de Sousa et al., 2018; Porcelli et al., 2018). In all, previous work has shown broad patterns of social dysfunction in schizophrenia (Porcelli et al., 2018; Velthorst et al., 2017), as well as in primary affective disorders such as major depression (Kupferberg et al., 2016; Velthorst et al., 2017) and bipolar disorder (Sanchez-Moreno et al., 2009; Velthorst et al., 2017). Yet, while symptoms of these disorders undoubtedly impact social functioning, the role of social cognitive deficits in the etiology of psychotic and affective symptoms remains elusive.

Schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD) display overlapping clinical symptoms, particularly in the mood and psychosis spectrum (Kempf et al., 2005; Pearlson, 2015). However, they also each have characteristic symptom patterns and show a different clinical course (Bora, 2015; Correll et al., 2007; Murray et al., 2004). It remains unclear whether they are discrete entities with distinct etiology and pathogenesis, or whether they are representative of a spectrum of mood-psychosis disorders.

More specifically, schizophrenia spectrum disorders, such as SZ (American Psychiatric Association, 2013a), are marked by significant disturbance in one or more of the following domains: positive symptoms

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(delusions, hallucinations, disorganizing thinking, disorganized or otherwise abnormal motor behavior), negative symptoms (such as lack of motivation, avolition, and anhedonia) and cognitive problems. Symptoms of affective disorders occur frequently, but whether these occur secondary to psychosis, or as a symptom dimension of psychosis itself remains unclear. This may perhaps vary between individuals (Upthegrove et al., 2016). By contrast, MDD (American Psychiatric Association, 2013b) is recognized primarily as an affective disorder. Core symptoms include depressed affect, anhedonia, feelings of worthlessness and/or guilt, sleep disturbance, cognitive impairment (inability to sustain attention, indecisiveness) and symptoms associated with psychomotor disturbance (excessive agitation or sluggishness). In a minority of individuals, psychotic symptoms may occur secondary to a depressive episode. BD (American Psychiatric Association, 2013c) is characterized by a phasic pattern of affective dysregulation, with both episodes of abnormal positive affect (mania) and bouts of depression occurring in succession or even coinciding in "mixed" episodes. Mania is defined as a state of consistently elevated affect and/or agitation, with increases in energy, self-esteem and risk-taking, and (psychotic-like) subjective symptoms such as pressure of speech, racing thoughts and distractibility. In addition, severely inflated self-esteem can induce psychosis-like reality distortion and may cause the individual to lapse into grandiose delusion. Identifying overlapping and distinct features of SZ, BD, and MDD necessitates the concurrent investigation of patients with these disorders (Correll et al., 2007). Comparisons between patients diagnosed with these disorders may be especially useful in delineating etiological differences and similarities between affective and psychotic symptomatology.

Previous work investigating social cognitive dysfunction in psychiatric disorders has often focused on 'Theory of Mind' (ToM). ToM refers to the understanding that other people have a mind of their own, with their own private intentions, beliefs and emotions (Marraffa, n.d.), and is thought to be particularly important for the successful maintenance of social contact. Its prime function is the inference of other people's mental and emotional states from social cues, such as body language, facial expressions and indirect language, as well as contextual information. Impairments in ToM can greatly hamper interpersonal communication, for instance as is seen in autism spectrum disorder (Barthélémy and Bonnet-Brilhault, 2016; Fernandes et al., 2018). Nevertheless, even though ToM impairments have been theorized to play a role in the development of affective and psychotic symptoms, there is no consensus on its precise involvement in the etiology of SZ, BD and MDD symptoms.

In this paper, we will give a systematic review of the currently available secondary literature (meta-analyses and literature reviews) on ToM impairment in affective-psychotic pathology, and we will attempt to discern separate patterns of dysfunction, as they may relate to different psychiatric disorders and symptom profiles. Since prior findings show that non-social cognitive deficits scale with the severity of psychotic symptoms (so that patients with BD perform worse than those with MDD on several tasks (Lee et al., 2018; Maalouf et al., 2010); those with schizoaffective disorder (Kuswanto et al., 2016) or psychotic BD (Bora, 2018) are more severely impaired than those with non-psychotic BD; and those with SZ show more severe impairments than those with schizoaffective disorders (Kuswanto et al., 2016)), we expect deficits in ToM to be correlated primarily with symptoms of psychosis across disorders. As such, we expect the largest deficits in ToM among patients primary psychotic disorders such as SZ, and more preserved ToM in primary affective disorders with low psychotic symptom load, such as non-psychotic forms of MDD.

2. Methods

2.1. Search strategy

A systematic search of existing review literature was conducted using the PubMed, Scopus, PsycInfo and Embase databases, entering the search terms "schizophrenia AND theory of mind", "major depressive disorder AND theory of mind", "bipolar disorder AND theory of mind"," schizoaffective disorder AND theory of mind", "psychosis AND theory of mind" and "mood AND theory of mind". In addition, combined search terms (e.g. "schizophrenia AND major depressive disorder AND theory of mind") were used to consider articles that characterized more than one of the aforementioned disorders, but those did not yield any additional results that were not already included in results for the disorder-specific searches. All authors were involved in the quality checking of articles returned using the search strategy outlined above. Of all articles that were possibly relevant to our study, only articles that were found by all three authors to conform to our inclusion criteria were included.

2.2. Inclusion criteria

For an article to be included in the current systematic review, it had to satisfy the following set of criteria:

1) The article is a literature review, a systematic review or a meta-analysis.
2) The article was published between January 2009 and January 2020
3) The article either

a) contains a review that focuses primarily on the characterization of Theory of Mind faculties in the disorder included in the search term or the extended phenotype thereof (such as high-risk cohorts, first-degree relatives)

or

b) contains a review about Theory of Mind in the disorder, but as a part of a review on a wider range of (social) cognitive functions

and deals primarily with the social cognitive profile associated with the disorder, rather than its neurobiological or genetic correlates or implications on treatment.

4) The article is in English.
5) The article was published in a peer-reviewed journal and is available in full online.

2.3. Approach

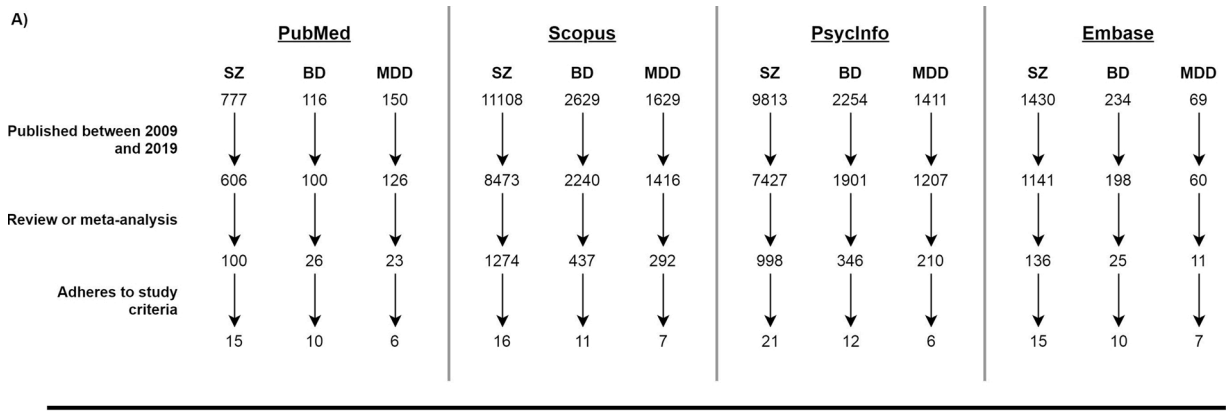
Before integrating the findings from the included meta-analyses and literature reviews we provide a general overview of number and types of publications with reference to the tables, followed by general comments on the ToM task on which the meta-analyses and literature reviews were based. Subsequently, per diagnosis we integrated the findings on 1) differences between patients and controls, 2) differences between subgroups of patients and controls, and 3) correlations between ToM performance and symptoms. Finally, we described the secondary literature that made a comparison between at least two of the three disorders of interest.

3. Results

3.1. Yield

A total of 44 articles satisfied our criteria (Fig. 1). Twenty-three of these concern ToM in schizophrenia spectrum disorders, six in major depression and associated disorders, and ten in bipolar spectrum disorders. Three studies compare ToM capabilities in patients with SZ to those in patients with BD, one compares patients with BD to patients with MDD, and another one compares between patients with all three illnesses. It shows that the vast majority of ToM studies is performed in SZ, followed by BD and the least studies have been carried out for MDD.

An overview of the literature considered in the current systematic review can be found in Tables 1 to 4 (which include studies on SZ, BD,



B)

SZ	BD	MDD	SZ & BD	SZ & MDD	BD & MDD	SZ & BD & MDD	Total
23	10	6	3	0	1	1	44

Fig. 1. Visualization of our search protocol. A targeted search was conducted using search terms containing "theory of mind" and one of the disorders specified above. A) shows the number of results per search term for each database, before and after applying study criteria. B) shows the total number of studies that satisfied our criteria for each diagnostic group, adjusted for duplicate results.
SZ = schizophrenia; BD = bipolar disorder; MDD = major depressive disorder.

MDD, and comparisons between disorders respectively). In the tables we summarize three types of findings, i.e. group comparison between patients and controls on general measures of ToM, group comparisons between patients and controls on specific subdomains of ToM, and clinical correlates of ToM impairment in patients only. In each table we first list the available meta-analyses, followed by systematic reviews and literature reviews. Within these categories, articles on patient groups are listed before those discussing first-episode and high-risk groups. Within clinical groups, articles are ordered by year of publication.

Before summarizing the disorder/symptom specific findings, we report our findings related to type of ToM that was considered in the included (meta-)reviews.

3.2. Note on constructs and tasks

The vast majority of the meta-analyses and literature reviews consider ToM as a single construct. A total of 13 reviews distinguish between cognitive and affective ToM (Berecz et al., 2016; Bora et al., 2016; Emre Bora et al., 2009a; Bora and Berk, 2016; Bora and Özerdem, 2017; Lahera et al., 2011; Mercer and Becerra, 2013; Samamé, 2013; Samamé et al., 2015, 2012; Schreiter et al., 2013; Song et al., 2015; Weightman et al., 2014) [SZ: n = 4, BD: n = 7, MDD: n = 4], while five reviews separate mentalizing from decoding tasks (Bora and Berk, 2016; Bora and Pantelis, 2013; Kupferberg et al., 2016; Lavoie et al., 2013; McKinnon et al., 2013) [SZ: n = 2, BD: n = 1, MDD: n = 2]. Four reviews take the difference between first, second or higher order ToM into account, which represents a measure of complexity (Bora et al., 2009b; Chan and Chen, 2011; Healey et al., 2016; Samamé et al., 2012) [SZ: n = 3, BD: n = 1, SZ&BD: n = 1]. Lastly, a distinction between visual and verbal task presentation is used in five reviews (Bora et al., 2016; Bora and Berk, 2016; Healey et al., 2016; Song et al., 2015; van Donkersgoed et al., 2015) [SZ: n = 3, BD: n = 1, MDD: n = 1].

3.3. Theory of mind in schizophrenia spectrum disorders

A total of 23 reviews were identified in which SZ is the central point of reference. However, several of the empirical studies that were included in these reviews also included individuals diagnosed with schizoaffective disorder (SZA, i.e. a lifetime pattern of schizophreniform symptoms with concurrent affective disturbance) or first episode psychosis (FEP, usually considered as a precursor to SZ). In addition, several reviews assess multiple disorders along the schizophrenia spectrum, e.g. including schizotypal personality disorder and delusional disorder (see Table 1, column 2).

3.3.1. ToM impairment in patients relative to controls

Four meta-analyses consistently reported a large-sized ToM deficit in SZ patients relative to controls, ranging from 0.80 to 1.45. Savla and colleagues (Savla et al., 2013) synthesized data from 50 ToM studies (n = 1,760) as part of a larger meta-analysis of social cognitive measures in patients with a diagnosis of SZ, SZA or FEP, reporting an effect size of 0.96 (reported as Hedges' g; a measure of effect size that is roughly similar to Cohen's d). Bora, Yücel & Pantelis (Bora et al., 2009a) meta-analyzed 1,181 individuals diagnosed with SZ, SZA or FEP and found decreased ToM in patients with an effect size of 1.21 (Cohen's d). Notably, this study showed that performance on the RMET (a visual task to assess affective ToM) was significantly less impaired than performance on cognitive ToM tasks. Further, the performance of a subsample of remitted patients was impaired (d = 0.80), but the effect size was significantly smaller than that of the sample as a whole. Song and colleagues (Song et al., 2015) investigated ToM in a set of studies conducted among 377 individuals diagnosed with SZ or SZA and, similar to Bora, Yücel & Pantelis (Bora et al., 2009a), reported a large group effect (Cohen's d = 1.27). However, they did not find a significant difference in effect size between cognitive (d = 1.20) and affective (d = 1.45), or between visual (d = 1.22) and verbal (d = 1.24) ToM tasks. Finally, one meta-analysis (Bora and Pantelis, 2013) assessed ToM in a first-episode cohort (n = 285) and found a similarly large effect size (Cohen's d = 1.11).

All literature reviews that assessed between-group differences concluded that some sort of deficit is present in SZ (Biedermann et al., 2012; Billeke and Aboitiz, 2013; Bora et al., 2009b; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013; Javed and Charles, 2018; Mondragón-Maya et al., 2017) and in FEP (Biedermann et al., 2012; Bora et al., 2009b; Healey et al., 2016; Javed and Charles, 2018; McCleery et al., 2014; Vyas et al., 2017), with several reviews reiterating findings that deficits in FEP resemble those in SZ (Healey et al., 2016; Vyas et al., 2017). Furthermore, it is suggested that deficits persist (albeit in an attenuated form) into the remitted phase of SZ (Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013). ToM abilities have been found to be largely stable in longitudinal studies of FEP (Healey et al., 2016). One review (Healey et al., 2016) suggested that

Table 1
Overview of reviews assessing Theory of Mind in schizophrenia spectrum disorders.

Study	Diagnoses included	Study type (if reported, number of patients)	Number of studies included	Clinical correlates of ToM impairment among patients only	Between-group comparisons of subdomains or specific tasks of ToM	Between-group comparisons of ToM performance
Bora et al. (2009a,b)	SZ, SZA, FEP	Meta-analysis (n = 1181)	36	N/A	RMET (d = 0.90) > HT/FB (d = 1.06-1.10).	d = 1.10 (HC > SZ) d = 1.21 (HC > aSZ) d = 0.80 (HC > rSZ)
Fett et al. (2011)	Non-affective psychosis	Systematic review and meta-analysis (n = 2692, ToM measures from 114 subjects used)	3 ToM studies (52 total)	Community functioning –	N/A	N/A
Savla et al. (2013)	SZ	Meta-analysis (n_{SZ} = 3901, ToM measures from 1760 subjects used)	50 ToM studies (112 total)	N/A	N/A	g = 0.96 (HC > SZ)
Ventura et al. (2013)	SZ	Meta-analysis (n_{SZ} = 7175, not exclusively ToM)	52 ToM studies (154 total)	Reality distortion ~ Disorganization + Negative symptoms + Non-social cognition –	N/A	N/A
Song et al. (2015)	SZ, SZA	Meta-analysis (n = 377)	13	N/A	aToM (d = -1.45) == cToM (d = -1.20) == veToM (d = -1.24) == viToM (d = -1.22).	d = -1.27 (HC > SZ)
De Sousa et al. (2019)	SSD	Meta-analysis (n = 9107, ToM measures from 3770 subjects)	59 ToM studies (123 total)	Formal thought disorder + Alogia + Disorganization + Age ~	N/A	N/A
Bora & Pantelis (2013)	FEP, cHR, SZfHR	Systematic review and meta-analysis (n_{total} = 3005 n_{FEP} = 285 n_{cHR} = 332 n_{SZfHR} = 2388)	10 (12 samples, SZfHR), 7 (cHR), 8 (FEP)	N/A	SZfHR specifically are impaired on ToM reasoning, but not decoding tasks.	d = 1.11 (HC > FEP) d = 0.45 (HC > cHR) d = 0.37 (HC > SZfHR)
Lavoie et al. (2013)	SZfHR	Meta-analysis (n_{SZfHR} = 3561, ToM measures from 2320 subjects used)	11 ToM studies (29 total)	N/A	d = 0.32 (decontextualized mentalizing) d = 0.62 (contextualized mentalizing)	d = 0.48 (HC > SZfHR) Deficits in SZfHR are intermediate to those in SZ and HC.
Van Donkersgoed et al. (2015)	cHR	Meta-analysis (n_{cHR} = 793, ToM measures from 372 subjects used)	7 ToM studies (17 total)	N/A	d = 0.52 (veToM) d = 0.33 (viToM; not significant)	d = 0.44 (HC > cHR)
Lee et al. (2015)	cHR	Meta-analysis (n_{cHR} = 1229, ToM measures from 382 subjects used)	8 ToM studies (22 total)	N/A	N/A	g = -0.43 (HC > cHR) Deficits in cHR are intermediate to those in SZ and SZfHR.
Mondragón-Maya, et al. (2017)	SZ, SZfHR, cHR	Systematic review	76 (not exclusively ToM studies)	N/A	N/A	ToM impairments reliably found in SZ, SZfHR and cHR.
Thompson et al. (2011)	cHR	Systematic review	2 ToM studies (7 total)	N/A	N/A	ToM impairments found in cHR, but evidence is inconsistent.
De Paula et al. (2015)	cHR	Systematic review	4 ToM studies (49 total)	N/A	N/A	ToM impairments reliably found in cHR.
Healey et al. (2016)	FEP	Systematic review	17 ToM studies, 16 unique samples. (48 total)	N/A	Significantly better performance on tasks assessing viTom or first order ToM, than on those assessing veToM or second order ToM.	ToM impairments reliably found in FEP and SZfHR. Deficits in FEP are similar in size to those in SZ and are stable over time.
Lincoln et al. (2017)	cHR	Systematic review	9 ToM studies (25 total)	N/A	Impairment is most severe on higher order tasks that assess veToM	ToM impairments reliably found in cHR.
Chan & Chen (2011)	SZ	Review	Not reported	Negative symptoms + Disorganization + Paranoid delusions +/~ Passivity symptoms ~	Paranoid symptoms may be related specifically to deficits in second order ToM.	N/A
Biedermann et al. (2012)	SZ, cHR, SZfHR, FEP	Review	35	N/A	N/A	ToM impairments reliably found in SZ.
Billeke & Aboitiz (2013)	SZ	Review	Not reported	N/A	N/A	ToM impairments reliably found in SZ.
Gavilán Ibanez & García-Albea Ristol (2013)	SSD	Review	Not reported	N/A	N/A	ToM impairments reliably found in aSZ, and in attenuated form in SZfHR, SZT and rSZ.
Dimopoulou et al. (2017)	SSD	Review	150 (not exclusively ToM studies)	N/A	N/A	ToM impairments reliably found along the schizophrenia spectrum,

(*continued on next page*)

Table 1 (*continued*)

Study	Diagnoses included	Study type (if reported, number of patients)	Number of studies included	Clinical correlates of ToM impairment among patients only	Between-group comparisons of subdomains or specific tasks of ToM	Between-group comparisons of ToM performance
						including SZfHR, SZT, cHR, FEP and chronic SZ groups.
Javed & Charles (2018)	SZ	Review	139 (not exclusively ToM studies)	N/A	N/A	ToM impairments reliably found in SZ.
McCleery et al. (2014)	FEP, cHR, SZfHR	Review (book chapter)	Not reported	N/A	N/A	ToM impairments reliably found in FEP, and in attenuated form in cHR and SZfHR.
Vyas et al. (2017)	Early-onset schizophrenia, cHR, SZfHR, FEP	Review	133	N/A	N/A	ToM impairments reliably found in FEP and SZfHR. Deficits in FEP are similar in size to those in SZ. Intermediate deficits in SZfHR.

Table 2
Overview of reviews assessing Theory of Mind in bipolar and related disorders.

Study	Diagnoses included	Study type (if reported, number of patients)	Number of studies included	Correlations with ToM impairment among patients	Task/domain comparisons in patients	Between-group comparisons of ToM performance
Samamé et al. (2012)	BD (euthymic)	Systematic review and meta-analysis (n = 650, ToM measures from 306 subjects used)	9 ToM studies (20 total)	N/A	d = 0.75 (basic ToM) d = 0.86 (complex ToM) d = 0.40 (RMET)	d = 0.50 – 0.79 (HC > rBD)
Samamé et al. (2015)	rBD	Meta-analysis (n_{BD} = 712, ToM measures from 374 subjects used)	11 ToM studies (19 total)	N/A	Significant impairments on cognitive FP, but not affective FP tasks.	g = 0.27 – 0.58 (HC > rBD)
Bora et al. (2016)	BD (euthymic, subsyndromal and acute)	Meta-analysis (n = 1214)	34	N/A	aToM (d = 0.46) == cToM (d = 0.68); veToM (d = 0.58) == viToM (d = 0.58)	d = 0.63 (HC > BD) d = 1.23 – 1.31 (HC > aBD) d = 0.50 (HC > rBD) d = 0.72 (HC > ssBD)
Bora and Özerdem (2017)	BDfHR	Meta-analysis (n = 728, ToM measures from 216 subjects used)	16 (not exclusively ToM studies)	N/A	Significant impairments both on HT (cToM) and RMET (aToM).	d = 0.34 (HC > BDfHR)
Mercer & Becerra (2013)	rBD	Systematic review	3 ToM studies (34 total)	N/A	Both aToM and cToM may be impaired.	ToM impairments reliably found in BD.
Samamé (2013)	BD (euthymic, depressed, manic)	Systematic review	15 ToM studies (51 total)	N/A	Significant impairment on cToM, but not on aToM tasks.	ToM impairments reliably found in all mood states of BD.
Lahera et al. (2011)	BD	Review (book chapter)	Not reported	N/A	Significant impairments on cToM, but not on aToM tasks.	ToM impairments reliably found in BD. Deficits in mania are larger than those in depression.
Simon et al. (2011)	BD	Review	11 ToM studies (64 total)	N/A	N/A	ToM impairments reliably found in all mood states of BD.
McKinnon et al. (2013)	BD (euthymic, subsyndromal, acute)	Review	Not reported	N/A	rBD are impaired only on tasks that place high demand on cognitive resources, but not on less demanding ToM tasks.	ToM impairments reliably found in rBD and subsyndromal patients
Tsitsipa & Fountoulakis (2015)	BD	Review	Not reported	N/A	N/A	ToM impairments reliably found in BD.

first-order ToM reasoning may be intact in FEP, whereas performance on verbal and second-order tasks was reduced in patients compared to controls.

3.3.2. *ToM and the extended schizophrenia spectrum*

Several reviews assessed ToM capabilities in those at high risk (HR) for developing SZ spectrum disorders, such as first-degree relatives of SZ patients (who are familial high-risk [fHR] to develop SZ) and clinical high risk (cHR) groups (people who display prodromal symptoms but have not yet experienced a psychotic break), or those with schizotypal personality disorder (a personality disorder which bears considerable genetic and symptomatic overlap with SZ but somehow rarely lapses into full-on psychosis) (American Psychiatric Association, 2013d).

Significant ToM deficits have been found in unaffected fHR, with Bora and Pantelis (n = 2,388) (Bora and Pantelis, 2013) and Lavoie and colleagues (n = 2,320) (Lavoie et al., 2013) both reporting small to medium sized deficits (Cohen's d = 0.37 and 0.48 respectively). This finding is corroborated by several literature reviews (Biedermann et al., 2012; Bora et al., 2009b; Dimopoulou et al., 2017; McCleery et al., 2014; Mondragón-Maya et al., 2017; Vyas et al., 2017). Lavoie and colleagues (Lavoie et al., 2013) noted that age-related effects may have confounded their results, as parents of offspring with SZ appear to underperform adult siblings of patients with SZ.

In addition, three meta-analyses (Bora and Pantelis, 2013; Lee et al.,

Table 3
Overview of reviews assessing Theory of Mind in major depressive and related disorders.

Study	Diagnoses included	Study type (if reported, number of patients)	Number of studies included	Correlations with ToM impairment among patients	Task/domain comparisons in patients	Between-group comparisons of ToM performance
Bora & Berk (2016)	MDD (including PDD)	Meta-analysis (n = 613)	18	N/A	Decoding (d = 0.44) == mentalizing (d = 0.50); aToM (d = 0.52) == cToM (d = 0.49); viToM (d = 0.53) == veToM (d = 0.38)	d = 0.58 (HC > aMDD)
Schreiter et al. (2013)	MDD, subclinical dysphoria	Systematic review	37 (not exclusively ToM studies)	N/A	RMET (aToM) performance may be enhanced in MDD.	Cognitive empathy impairments reliably found in MDD.
Weightman et al. (2014)	MDD (acute and remitted)	Systematic review	31 (not exclusively ToM studies)	N/A	aToM impairments consistently reported in MDD; findings on cToM are inconsistent.	ToM impairments reliably found in aMDD, possibly in rMDD.
Berecz et al. (2016)	Unipolar depressive disorders	Systematic review	32	N/A	RMET (aToM) performance may be enhanced in subclinical groups.	ToM impairments reliably found in aMDD, possibly in rMDD.
Gadassi & Rafaeli (2015)	MDD	Review	Not reported	N/A	N/A	ToM impairments reliably found in MDD. ToM performance may be enhanced in rMDD.
Kupferberg et al. (2016)	MDD	Review	Not reported	N/A	Impairment may be specific to mentalizing tasks.	ToM impairments and deficits in empathy reliably found in MDD.

Table 4
Overview of reviews comparing Theory of Mind faculties between two or more of the specified disorders.

Study	Diagnoses included	Study type (if reported, number of patients)	Number of studies included	Correlations with ToM impairment among patients	Task/domain comparisons in patients	Between-group comparisons of ToM performance
Bora & Pantelis (2016)	SZ, BD	Meta-analysis (n_{BD} = 1075, n_{SZ} = 1301, ToM measures available from 674 SZ and 535 BD subjects)	16 ToM studies (26 total)	N/A	N/A	d = 0.57 (BD > SZ)
Bora, Yücel and Pantelis (2009)	SSD, BD	Systematic review	12 (SZ), 6 (FEP/cHR), 9 (SZfHR), 9 (BD/psychotic mood disorder), 2 (DD), 6 (schizotypy)	N/A	Specifically in cHR, impairments may be restricted to complex ToM tasks.	ToM impairments reliably found along the schizophrenia spectrum and in BD. Deficits in SZfHR and cHR are milder than those in SZ and FEP.
Mitchell & Young (2016)	BD, SZ	Systematic review	22 (BD) 15 (BD & SZ)	N/A	N/A	ToM impairments reliably found across mood states in BD. Deficits in BD are smaller than those in SZ.
Szmulewicz et al. (2017)	MDD, BD	Systematic review	1 ToM study (10 total)	N/A	N/A	ToM performance in rBD, rMDD, HC does not differ significantly.
Hoertnagl & Hofer (2014)	SZ, MDD, BD	Review	47 (not exclusively ToM studies)	N/A	N/A	ToM impairments reliably found in SZ, BD and MDD.

2015; van Donkersgoed et al., 2015) assessed ToM performance among cHR individuals (n = 332 – 382), and these all revealed significant small to medium deficits compared to healthy controls (Cohen's d = 0.43-0.45). Van Donkersgoed and colleagues (van Donkersgoed et al., 2015) reported that performance on verbal, but not visual, tasks is often significantly impaired, although the authors suggest this may be due to lack of statistical power or due to the less cognitively demanding nature of visual tasks. Literature reviews confirm this pattern of findings of attenuated ToM impairment in clinical high-risk groups (Bora et al., 2009b; de Paula et al., 2015; Dimopoulou et al., 2017; Lincoln et al., 2017; McCleery et al., 2014; Mondragón-Maya et al., 2017; Thompson et al., 2011; Vyas et al., 2017). Interestingly, there appears to be no correlation between ToM performance and risk of conversion in cHR groups (de Paula et al., 2015; Lee et al., 2015; McCleery et al., 2014; van Donkersgoed et al., 2015).

Findings with regards to schizotypal traits are scarce, but point towards the presence of a ToM deficit, with two reviews reporting significant deficits (Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013) and one reporting mixed findings (Bora et al., 2009b).

3.3.3. Clinical correlates of ToM in schizophrenia

In addition to comparisons between diagnostic groups and controls, many reviews also aimed to disentangle the relationships between deficits in ToM and clinical variables, such as functional outcome, non-social cognition, and psychotic symptom dimensions.

Several studies support an association between reduced ToM performance and poor functional outcome in schizophrenia spectrum disorders (Dimopoulou et al., 2017; Javed and Charles, 2018; McCleery et al., 2014; Mondragón-Maya et al., 2017), with two noting that poor ToM could serve as a mediator between non-social cognitive deficits and functional outcome (Dimopoulou et al., 2017; Javed and Charles, 2018). In addition, using a meta-analysis, Fett and colleagues (Fett et al., 2011) aimed to unravel the relationship between cognitive functioning and functional outcome in non-affective psychosis, and found that mentalizing skills predicted community functioning better than any other

social or non-social cognitive measure assessed.

Moreover, most reviews suggest an association between social and non-social cognitive deficits (Bora et al., 2009a; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013; Healey et al., 2016; Lavoie et al., 2013; Lee et al., 2015; Ventura et al., 2013). The majority report modest correlations and argue that non-social cognitive deficits are thus unlikely to fully explain the mentalizing deficit. This has led some to suggest that although intact cognition is a prerequisite for adequately functioning ToM, it is not sufficient (Gavilán Ibáñez and García-Albea Ristol, 2013). This may explain why several reviews found no correlation between social and non-social cognition in SZ (Billeke and Aboitiz, 2013; Song et al., 2015) or in HR (Vyas et al., 2017) groups.

Significant correlations are found between severity of all three major symptom dimensions and ToM, so that poor ToM is associated with more pronounced symptoms (Dimopoulou et al., 2017). However, relationships with negative (Healey et al., 2016; Mondragón-Maya et al., 2017; Ventura et al., 2013) and disorganized (de Sousa et al., 2019; Ventura et al., 2013) symptoms are reported more frequently than with positive (Healey et al., 2016; Mondragón-Maya et al., 2017) symptoms.

Interestingly, the authors of a recent meta-analysis found associations between reduced ToM capabilities and higher scores on three separate constructs of thought disorder (de Sousa et al., 2019) (disorganization, formal thought disorder and alogia). The authors postulated that loss of ToM causes a communication breakdown (interpreted as disorganized thought) between a patient and a listener because the patient is unable to take the listener's perspective.

None of the five studies that assessed the relationship between demographic variables (age, sex, years of education) and ToM performance reported significant associations (de Sousa et al., 2019; Savla et al., 2013; Song et al., 2015; van Donkersgoed et al., 2015; Vyas et al., 2017).

3.4. Theory of mind in bipolar disorder

Ten reviews were identified on BD. Since only two (Samamé, 2013; Simon et al., 2011) reviews distinguish between BD-I and BD-II, we limit ourselves to making statements about bipolar spectrum disorders in general.

3.4.1. ToM impairment in patients relative to controls

Three meta-analyses were available, reporting effect sizes between 0.27 and 1.31 depending on the clinical presentation of the patients and the tasks used. Bora, Bartholomeusz & Pantelis (Bora et al., 2016) assessed ToM capabilities in groups of acute, subsyndromal and euthymic BD patients as compared to healthy controls. Their results indicated a significant, medium-sized ToM impairment when all groups were taken together (Cohen's d = 0.63). When the groups were compared, acute symptomatic BD patients (d = 1.23) had a significantly larger ToM impairment than subsyndromal (d = 0.72) or euthymic patients (d = 0.50). When only acutely manic patients were considered, the effect size of the impairment was in the higher range (d = 1.31), suggesting a smaller effect size during the depressive phase. No significant differences in performance between cognitive and affective ToM or between verbal and visual ToM tasks were observed.

In two meta-analyses Samamé and colleagues (Samamé et al., 2015, 2012) also demonstrated significant deficits during the euthymic phase, with effect sizes ranging between d = 0.27 and d = 0.79 depending on the strictness of remission criteria, the task used and the specific domain assessed. In both meta-analyses, performance on affective tasks, such as affective faux-pas and the RMET, was largely preserved, whereas medium-to-large impairments were found for more cognitively oriented tasks.

Five literature reviews (Lahera et al., 2011; McKinnon et al., 2013; Samamé, 2013; Simon et al., 2011; Tsitsipa and Fountoulakis, 2015) in patients in the acute phase of the illness indicate that BD is consistently associated with ToM impairments, with two of them noting that the cognitive domain of ToM appears to be specifically affected (Lahera et al., 2011; Samamé, 2013). Furthermore, Lahera and colleagues (Lahera et al., 2011) noted that impairments during a manic episode were larger than in those who experienced a depressive phase.

All reviews that considered ToM scores during bipolar euthymia suggest a similar pattern, concluding that some form of impairment persists beyond the acute phase (Lahera et al., 2011; McKinnon et al., 2013; Mercer and Becerra, 2013; Samamé, 2013; Simon et al., 2011). McKinnon, Cusi & MacQueen (McKinnon et al., 2013) reported that euthymic patients specifically display deficits on ToM tasks that involve complex reasoning.

3.4.2. ToM and the extended bipolar spectrum

A meta-analysis including unaffected first-degree relatives of patients with BD reported a small but significant impairment in those with fHR (Cohen's d = 0.34), with significantly reduced performance on both the RMET (d = 0.21) and HT (d = 0.34) compared to controls (Bora and Özerdem, 2017).

3.4.3. Clinical correlates of ToM in bipolar disorder

Six literature reviews and meta-analyses conclude that in BD patients, lower ToM scores are associated with poor performance on measures of non-social cognition (Bora et al., 2016; Lahera et al., 2011; Samamé, 2013; Samamé et al., 2015; Simon et al., 2011; Tsitsipa and Fountoulakis, 2015), whereas a review in unaffected relatives suggested a null effect (Bora and Özerdem, 2017).

The two reviews that reported on greater ToM impairment during the manic phase of BD (Bora et al., 2016; Lahera et al., 2011) found significant associations of impaired ToM performance with higher scores on the YMRS during mania (Bora et al., 2016) and with a higher number of previously experienced manic episodes (Lahera et al., 2011). However, a meta-analysis found no associations between ToM capabilities and illness duration, the number of episodes experienced, or lithium dosage (Samamé, 2013), suggesting that in patients with BD, ToM deficits are stable over time and illness course and possibly irresponsive to medication.

In the three studies that assessed relationships between demographic variables and ToM, no significant associations were reported (Bora et al., 2016; Samamé et al., 2015, 2012).

3.5. Theory of mind in depressive disorders

A total of six reviews were identified. Two reviews (Berecz et al., 2016; Bora and Berk, 2016) also included primary studies on persistent depressive disorder (PDD) or dysthymia (both terms refer to a depressive illness with a chronic, non-episodic course), in addition to studies in pure MDD. Two reviews (Berecz et al., 2016; Schreiter et al., 2013) also discuss studies in participants suffering from subclinical depressive symptoms. Moreover, unless otherwise specified, this section will deal with primary, non-psychotic depression.

3.5.1. ToM impairment in patients relative to controls

One recent meta-analysis (Bora and Berk, 2016) indicated significant, medium-sized ToM impairment in patients suffering from MDD and PDD (Cohen's d = 0.51). No significant differences in effect size were found between the cognitive (Cohen's d = 0.49) and affective (d = 0.52) ToM domains, decoding (d = 0.44) and reasoning (d = 0.50) tasks, and between the visual (d = 0.53) and verbal (d = 0.38) modalities.

Five literature reviews pointed towards some sort of ToM deficit during acute MDD (Berecz et al., 2016; Gadassi and Rafaeli, 2015; Kupferberg et al., 2016; Schreiter et al., 2013; Weightman et al., 2014). Kupferberg, Bicks & Hasler (Kupferberg et al., 2016) argued that ToM impairment in MDD is specific to the ToM reasoning domain. In contrast, decoding of mental states from observable cues was generally preserved in MDD patients. Weightman, Air & Baune (Weightman et al., 2014) asserted that there is sufficient evidence for impairments in affective

ToM as measured by the RMET, while evidence on cognitive ToM is more equivocal. Finally, one review found deficits on several constructs of cognitive empathy (i.e. perspective taking, empathetic accuracy and ToM) in MDD patients (Schreiter et al., 2013).

Evidence regarding ToM performance in the remitted phase of MDD is contradictory. While some reviews indeed suggest that people with a history of MDD are impaired on mental state reasoning (Berecz et al., 2016; Weightman et al., 2014), it is also noted that people with a past MDD outperform healthy controls on the RMET (Berecz et al., 2016; Gadassi and Rafaeli, 2015). In this context, one of the reviews (Berecz et al., 2016) suggested that both impaired and enhanced ToM could be a risk factor for the development of MDD, as both could lead one to excessively ruminate on subtle social cues and thereby contribute to social withdrawal.

3.5.2. ToM and the extended depressive spectrum

To our knowledge, none of the reviews assessed ToM skills in healthy relatives of MDD patients. However, two reviews (Berecz et al., 2016; Schreiter et al., 2013) did assess ToM capabilities in persons exhibiting subthreshold depressive symptoms (or dysphoria). They report a general trend of enhanced RMET performance in dysphoric individuals compared to controls, although some of the included empirical studies suggest an opposite effect.

3.5.3. Clinical correlates of ToM in major depression

Although limited, some evidence exists for associations between clinical characteristics and mentalizing abilities in MDD. Reduced ToM correlated with increased depressive symptom severity (Bora and Berk, 2016; Schreiter et al., 2013; Weightman et al., 2014) and social dysfunction (Gadassi and Rafaeli, 2015; Weightman et al., 2014), with one review suggesting that an interpersonal perception construct (including ToM) mediates between social dysfunction and depression scores (Gadassi and Rafaeli, 2015). Also, associations were reported with psychotic depressive symptoms (Berecz et al., 2016; Weightman et al., 2014), but research is limited and non-social cognitive deficits (i.e. loss of verbal fluency) may confound this relationship (Berecz et al., 2016).

Two articles reported on the relationship between non-social cognitive impairments and deficits in ToM. Both concluded that generalized cognitive deficits appear to be associated with ToM impairment in patients with MDD (Bora and Berk, 2016; Schreiter et al., 2013).

3.6. Transdiagnostic comparisons

Five literature reviews and meta-analyses directly compared ToM capabilities between two or more of the disorders discussed above. Of these five, three articles included empirical studies on two or more patient groups (i.e. primary studies reporting on group differences between patients with SZ and BD (Bora and Pantelis, 2016; Mitchell and Young, 2016); BD and MDD (Szmulewicz et al., 2017)), while two reviews included primary studies assessing a single disorder, and compared between disorders post-hoc (i.e. comparisons between primary studies on BD and SZ (Bora et al., 2009b); SZ, BD and MDD (Hoertnagl and Hofer, 2014)).

BD and SZ: Two literature reviews and one meta-analysis compared between patients with BD and SZ. One review (Mitchell and Young, 2016) and one meta-analysis (Bora and Pantelis, 2016) assert that ToM deficits in patients with SZ are more severe than those in patients with BD ($d = 0.57$) (Bora and Pantelis, 2016). In the literature review (Mitchell and Young, 2016), it is asserted that the severity of positive symptoms (including forms of thought disorder) predicts ToM performance regardless of diagnosis, offering at least a partial explanation for differences in ToM impairment between disorders. In the meta-analysis (Bora and Pantelis, 2016), it was found that between-group differences in demographic and clinical variables (including the positive symptom dimension) did not significantly explain the difference in ToM between patient groups. A second literature review (Bora et al., 2009b), which assessed ToM in a range of SZ spectrum disorders as well as BD, concluded that there are indeed impairments related to both the SZ spectrum disorders and BD, but this review did not compare the severity of the impairment between diagnoses. Furthermore, the authors speculated that generalized cognitive deficits may drive ToM deficits only in the milder SZ spectrum disorders and BD but not in the more severe phenotype of SZ.

BD and MDD: One review (Szmulewicz et al., 2017) assessed differences in social cognitive skills between MDD and BD, but included only a single primary ToM study (Purcell et al., 2014). This study did not report significant group differences between patients with remitted MDD, patients with remitted BD, and unaffected controls.

SZ, BD and MDD: The literature review by Hoertnagl & Hofer (Hoertnagl and Hofer, 2014), that considered social cognition in all three disorders discussed here, concluded that deficits occur in SZ, BD and MDD, and that the severity of the ToM deficit differs between disorders. However, no conclusions were drawn as to the magnitude of the ToM impairments, and no direct comparisons between the disorders were made.

4. Discussion

In the current systematic review, we synthesized the available secondary literature investigating Theory of Mind (ToM) capabilities in patients suffering from a range of affective and psychotic spectrum disorders. For the first time, we aimed to elucidate the specific patterns of ToM impairment that characterize them at the level of categories (or diagnoses) and symptoms. As most available secondary literature touches only on a single diagnostic category, the comparative, transdiagnostic approach of the current review may shed new light on the association between social cognition and symptoms of severe mental illness across diagnoses. The existing body of evidence suggests that significant impairments in ToM mentalizing and decoding exist in major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ), as well as in the broader spectrum disorders and at-risk groups. Deficits in ToM may thus be a core feature of both psychotic and affective psychopathology. However, effect sizes found in patients with SZ tend to be larger than those found in patients with MDD, with BD occupying an intermediate position on this spectrum. Moreover, in SZ patients, ToM deficits were more pronounced in the presence of increased negative or disorganized symptoms, and in BD patients when they experienced high levels of manic symptoms. In addition, it appears that deficits persist beyond the symptomatic phase in both SZ and BD, and deficits are consistently found in unaffected family members of patients with BD or SZ. Together, this suggests that ToM deficits as seen in BD and SZ consist at least in part of a trait component and may thus represent an endophenotype that is associated with risk of developing these illnesses. By contrast, in patients with MDD, impairments of ToM appear to be largely state dependent, and cohere mostly with the expression of depressive symptoms.

4.1. Impairment in diagnostic groups and relationship with symptoms

ToM deficits appear to be a marker of the schizophrenia spectrum disorders and their extended phenotype, encompassing familial and clinical at-risk groups as well as associated personality traits, and are likely to cohere with symptom expression to some extent. Specifically, in SZ patients, literature reviews and meta-analyses consistently indicate large-sized impairments in ToM (Biedermann et al., 2012; Billeke and Aboitiz, 2013; Bora et al., 2009b; Bora et al., 2009a; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013; Javed and Charles, 2018; Mondragón-Maya et al., 2017; Savla et al., 2013; Song et al., 2015). The relatively large spread in effect sizes may be explained by the heterogeneity within patient samples, as many samples included in the individual empirical studies consist of both symptomatic and remitted

patients. Indeed, when clinical groups along the SZ-risk and/or symptom severity spectrum are compared, a gradient can be observed, with the strength of the mentalizing impairment increasing along with the increase in psychotic symptomatology (see Fig. 2a). For example, patients who experience a first-episode of psychosis patients appear to have an impairment that is similar in size to that in those with a diagnosis of SZ (Bora et al., 2009b; Bora and Pantelis, 2013; Healey et al., 2016; McCleery et al., 2014; Vyas et al., 2017). Intermediate effect sizes are reported for unaffected first-degree relatives (Bora et al., 2009b; Bora and Pantelis, 2013; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013; Lavoie et al., 2013; McCleery et al., 2014; Mondragón-Maya et al., 2017; Vyas et al., 2017), high-risk groups (Bora et al., 2009b; Bora and Pantelis, 2013; de Paula et al., 2015; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013; Lee et al., 2015; Lincoln et al., 2017; McCleery et al., 2014; Mondragón-Maya et al., 2017; Thompson et al., 2011; van Donkersgoed et al., 2015), and remitted patients (Bora et al., 2009a; Gavilán Ibáñez and García-Albea Ristol, 2013) compared to matched controls. Some evidence exists for compromised ToM in people with high schizotypy, although the severity of this deficit remains to be determined (Bora et al., 2009b; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013).

Interestingly, correlations with ToM scores have been found consistently for the negative (Healey et al., 2016; Mondragón-Maya et al., 2017; Ventura et al., 2013) and disorganized (de Sousa et al., 2019; Ventura et al., 2013) symptom dimensions, so that more pronounced ToM deficits correlate with higher levels of symptoms, whereas findings for reality distortion (Chan and Chen, 2011; Healey et al., 2016; Mondragón-Maya et al., 2017; Ventura et al., 2013) are more equivocal, suggesting that ToM impairments may not be as strongly associated with the development of positive symptoms. Surprisingly, there is no evidence that the presence or extent of a ToM deficit predicts conversion to psychosis in high-risk cohorts (de Paula et al., 2015; Lee et al., 2015; McCleery et al., 2014; Mondragón-Maya et al., 2017; van Donkersgoed et al., 2015), although reviews and meta-analyses regarding conversion are limited by a lack primary studies in this area as well as by small sample sizes. Large-scale prospective research is needed to properly address this question.

Studies indicate that, like patients with SZ, patients with mood disorder, i.e. BD or MDD, are impaired on ToM tasks. Deficits have been found throughout all mood states and the severity of impairment increases with the expression of symptoms, so that symptomatic patients are most strongly impaired (Bora et al., 2016; Lahera et al., 2011; Samamé, 2013; Simon et al., 2011; Tsitsipa and Fountoulakis, 2015). However, the pattern of expression differs between mania and depression (see Figs. 2b and 2c). That is, patients in a manic episode perform worse than patients in a depressive episode (Bora et al., 2016; Lahera et al., 2011). This may be explained by a shift towards the psychotic end of the affective-psychotic spectrum during mania, thereby approaching the effect sizes as found in SZ. It has been observed that BD patients who predominantly experience manic episodes have a significantly increased lifetime incidence of psychotic symptoms as compared to those without a dominant manic polarity (Pallaskorpi et al., 2019). Also, an estimated 50% of BD-I patients experience psychotic symptoms during the prodrome of a manic episode (Mansell and Pedley, 2008). ToM deficits in euthymic patients with BD appear to be less severe (Bora et al., 2016; Lahera et al., 2011; McKinnon et al., 2013; Mercer and Becerra, 2013; Samamé, 2013; Samamé et al., 2015, 2012; Simon et al., 2011), but larger than those in unaffected relatives (Bora and Özerdem, 2017), who perform at an intermediate level compared to euthymic patients and matched controls. Although research in at-risk groups is scarce, there is preliminary evidence that individuals at an enhanced familial risk of BD have impaired ToM (Bora and Özerdem, 2017), suggesting that, similar to SZ, impaired ToM may serve as an endophenotype of the bipolar spectrum.

In patients with MDD, ToM deficits are consistently reported in the symptomatic phase (Berecz et al., 2016; Bora and Berk, 2016; Gadassi and Rafaeli, 2015; Kupferberg et al., 2016; Schreiter et al., 2013; Weightman et al., 2014), and these deficits were more pronounced with more severe symptoms (Bora and Berk, 2016; Schreiter et al., 2013; Weightman et al., 2014). For patients who are in remission, findings are

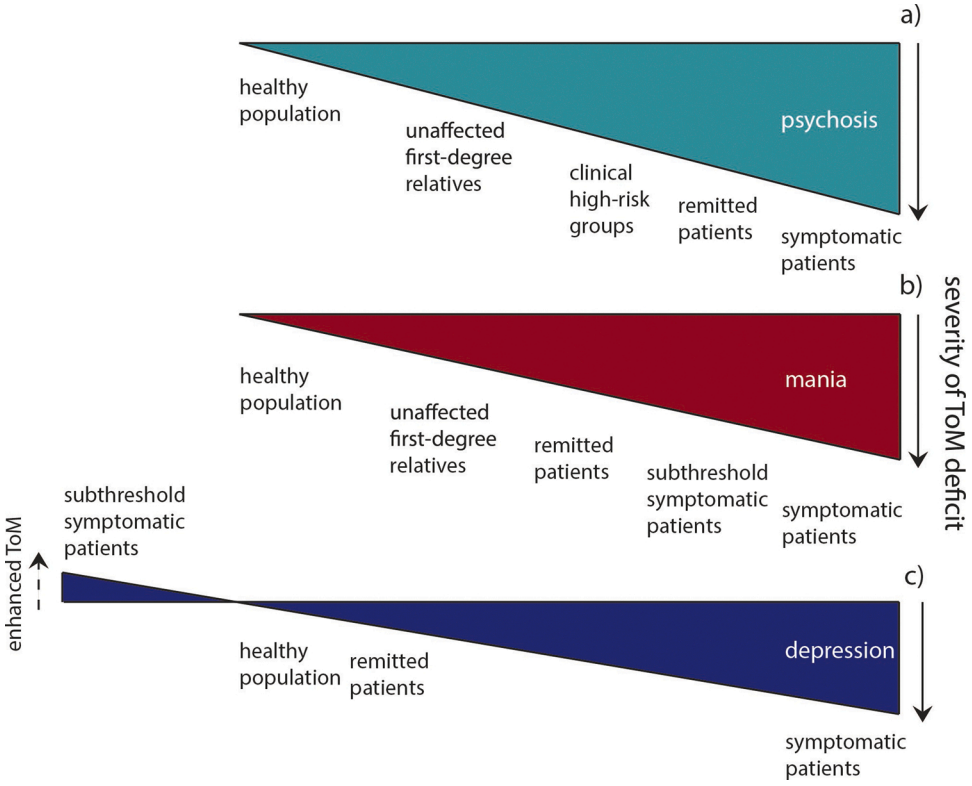


Fig. 2. Theory of Mind deficits in psychotic and affective disorders. Mentalizing impairments relate differentially to symptoms of psychosis, depression and mania. **a)** Psychotic symptom severity (or psychosis risk) scales along with the extent of the ToM impairment, as evidenced by the spread of effect sizes from the comparisons between patients along the psychosis risk spectrum and unaffected controls. **b)** The severity of manic symptomatology appears to correlate directly with the size of the ToM impairment. Symptomatic patients display a ToM deficit similar in size to that observed in SZ patients during an acute psychotic episode, whereas subsyndromal and euthymic groups, as well as healthy relatives of patients with BD show increasingly smaller, but significant deficits. **c)** Although MDD coincides with impairments in ToM, those who are in remission may have a close to normal ToM. Persons who suffer from subthreshold symptoms of dysphoria may even exhibit enhanced performance on affective ToM tasks when compared to the healthy population.

less consistent. Some studies show support for a persisting deficit (Berecz et al., 2016; Weightman et al., 2014), although lingering subclinical symptoms may exert a confounding effect and lead to subtle ToM deficits. As little ToM research has been conducted in remitted and at-risk individuals, it remains unclear whether MDD is associated with trait-level ToM deficits. It is imperative that these groups are investigated in greater detail, as they may offer crucial insights into the temporal relationship between mentalizing capabilities and depressive symptomatology.

Interestingly, evidence exists that those suffering from a subclinical form of dysphoria *outperform* controls to some extent on the RMET (Berecz et al., 2016; Gadassi and Rafaeli, 2015) (although no such findings have been reported in the cognitive ToM domain). A possible explanation might be that enhanced affective ToM performance in subclinical depression may simply be the result of an interaction between the negativistic biases associated with depressed affect (Kupferberg et al., 2016; Weightman et al., 2014) and the positivistic cognitive biases found in the general population (Moore and Fresco, 2012). Positivistic cognitive biases can be conceptualized as a relative deficit in the recognition of negative emotional cues. Indeed healthy individuals have been shown to interpret ambiguous emotional cues as having a positive valence (Moore and Fresco, 2012). Perhaps, the increased attention to negative emotional information associated with subclinical depression or dysphoria (Kupferberg et al., 2016; Weightman et al., 2014) facilitates the recognition and accurate interpretation of neutral and negative emotional content when it is present in low doses. The presence of this 'depressive realism' effect (Moore and Fresco, 2012) with respect to ToM remains to be verified and studied in more detail.

4.2. Role of non-social cognition and different types of ToM

Theory of Mind (ToM) is a hypothetical construct that was originally postulated within the context of philosophy of mind (Marraffa, n.d.). Since it encompasses a wide variety of social cognitive skills, attempts have been made to dissect the construct and design assessment tools that isolate specific ToM faculties in order to make it more tangible and accessible to empirical research. However, it must be noted that ToM is still commonly assessed as if it were a single construct, even though this may confound results.

The distinction that is most readily used in the studies that were retrieved, is that between *affective* and *cognitive* ToM (Berecz et al., 2016; Bora et al., 2016; Bora et al., 2009a; Bora and Berk, 2016; Bora and Özerdem, 2017; Lahera et al., 2011; Mercer and Becerra, 2013; Samamé, 2013; Samamé et al., 2015, 2012; Schreiter et al., 2013; Song et al., 2015; Weightman et al., 2014). The major difference between the two is that affective ToM concerns the attribution of emotional states to oneself and others, whereas the cognitive component concerns the attribution of mental states such as intent, beliefs and knowledge to others (Westby, 2014). Several studies distinguished between *decoding* and *mentalizing* tasks (Bora and Berk, 2016; Bora and Pantelis, 2013; Lavoie et al., 2013; McKinnon et al., 2013), a distinction which is sometimes used interchangeably with the affective-cognitive dichotomy. *Mentalizing* describes one's capacity to reason with mental state concepts on a more abstract level, whereas *decoding* tasks require one to infer mental states from observable cues. Since mental state decoding is usually associated with the interpretation of emotional content, and mentalizing generally involves the attribution of propositional attitudes based on contextual information, most mentalizing tasks can be said to engage cognitive ToM faculties, whereas decoding tasks engage affective ToM.

As some social processes require more complex ToM involvement than others, some studies used comparative deficits in the different orders of ToM complexity to indicate the severity of the ToM impairment (Bora et al., 2009b; Chan and Chen, 2011; Healey et al., 2016; Samamé et al., 2012). "*First-order*" ToM concerns the direct inference of a feeling or mental state from another person's behavior, whereas "*second-order*" ToM refers to the inference of another person's beliefs concerning the thoughts and feelings of the self or a third person. "Higher-order" (or "complex") ToM is employed in the understanding of non-literal language through contextual information, as well as the interpretation of complex social relations (Westby, 2014). As ToM faculties develop during childhood in order of complexity, the assumption here is that higher-order ToM requires more sophisticated cognitive resources than first-order ToM, and that this higher-order faculty is more vulnerable and will degenerate earlier in the face of cognitive impairment. Therefore, higher-order ToM tasks may be more sensitive to subtle deficits in ToM whereas deficits on first-order ToM tasks may represent a more fundamental loss of social orientation.

Lastly, a distinction between *visual* and *verbal* task presentation is often used (Bora et al., 2016; Bora and Berk, 2016; Healey et al., 2016; Song et al., 2015; van Donkersgoed et al., 2015), as interpreting verbal social information (e.g. from a short story) may engage different cognitive faculties than visual social information (e.g. from body language), although little research backs this claim (Song et al., 2015).

The tasks most frequently used to assess ToM are the Reading the Mind in the Eyes Task (RMET: a visual task that is thought to assess affective ToM decoding), the False Beliefs Task (FBT: both visual and verbal versions exist, assessing first and second order cognitive ToM reasoning), the Hinting Task (HT: a verbal task measuring cognitive ToM reasoning) and the Faux-Pas Task (FPT: a verbal task that measures cognitive higher-order ToM reasoning) (Bora et al., 2009a).

At least in BD (Lahera et al., 2011; Samamé, 2013; Samamé et al., 2015, 2012) and SZ (Bora et al., 2009a; Bora and Pantelis, 2013) spectrum disorders, the cognitive domain of ToM appears to be more readily affected than the affective domain. Also, in patients with BD or SZ, second- and higher-order ToM faculties are compromised more strongly than first-order ToM processes (Bora et al., 2009b; Healey et al., 2016; Lahera et al., 2011; McKinnon et al., 2013). Perhaps this pattern of findings is unsurprising, given that the cognitive component of ToM draws more heavily on general cognitive skills (Westby, 2014). Similarly, higher-order ToM processes are cognitively more demanding (Westby, 2014). As significant cognitive impairment has been observed both in patients with SZ (Van Haren et al., 2019) and BD (Vreeker et al., 2016), impaired performance on cognitively challenging ToM tasks may simply reflect the presence of more generalized cognitive deficits in these disorders. Findings regarding deviations in specific ToM subdomains in patients with MDD are limited, and generally inconclusive. Indeed, while deficits in both affective and cognitive ToM appear to exist, the extent of these deficits remains unclear.

More generally speaking, there is tentative but mixed evidence for an association between ToM and non-social cognitive functioning in SZ (Billeke and Aboitiz, 2013; Bora et al., 2009a; Dimopoulou et al., 2017; Gavilán Ibáñez and García-Albea Ristol, 2013; Song et al., 2015; Ventura et al., 2013) and BD (Bora et al., 2016; Lahera et al., 2011; Samamé, 2013; Samamé et al., 2015; Simon et al., 2011; Tsitsipa and Fountoulakis, 2015), and possibly in MDD (Bora and Berk, 2016; Schreiter et al., 2013), suggesting that, although intact non-social cognition is required for proper social cognitive functioning, it is not sufficient. The social cognitive deficits found in these disorders can thus be explained only partly through general cognitive dysfunction.

However, there are some confounders worth considering when interpreting findings from the different ToM subdomains or tasks. First, there is still debate whether the RMET, the most frequently used measure of affective ToM, actually measures affective ToM or that it captures emotion recognition on a more basal level (Oakley et al., 2016). It is conceivable that individuals who lack adequate ToM can, to some extent, still *recognize* visual emotional cues, even if they cannot fully *grasp* what these emotions mean in relation to their social context. Thus, preserved performance on the RMET may not actually represent preserved affective ToM. Second, many of the cognitive ToM tasks are presented in the verbal modality (such as the HT or FBT) rather than visually (like the affective RMET), hampering the interpretability of findings within subdomains. For example, in SZ, performance on

visually presented tasks is less impaired than that on verbal tasks (Healey et al., 2016; van Donkersgoed et al., 2015), possibly due to the relatively higher cognitive demand placed on the interpretation of verbal information. Thus, task modality may act as a confounder when assessing cognitive and affective ToM tasks separately, and vice versa. Consequently, findings with respect to deficits in specific subdomains of ToM in patients with diagnoses across the affective-psychotic spectrum should be interpreted with caution.

4.3. Future considerations

In order to further unravel the etiological involvement of ToM deficits in symptoms of affective disorder and psychosis, several lines of research could be pursued.

First, there is a relative lack of primary studies that include patients with a variety of disorders along the mood-psychosis spectrum. In order to properly disentangle the discrete patterns of ToM impairment found in psychotic and affective disorders, more studies should aim to directly assess differences in performance (in association with specific symptoms) between patients with these disorders.

Second, it remains unclear whether ToM impairments represent a trait marker of MDD, and evidence pertaining to BD is still meagre, as very few studies have been conducted in individuals at familial or clinical high risk of unipolar and bipolar affective disorders. Furthermore, strict criteria should be enforced when limiting the investigation to remitted patients, as ToM may be affected in those experiencing subclinical depressive symptoms during remission.

Third, more longitudinal studies of high-risk groups, transdiagnostically, should be conducted, as to delineate whether ToM deficits predate, predict, and possibly drive conversion to psychosis or mood disorders.

Fourth, in MDD specifically, there may be a significant difference in impairment between affective and cognitive, or decoding and mentalizing constructs, due to the presence of an affect-congruent bias in the interpretation of emotional cues. Although such a bias is well documented in other social cognitive areas (Kupferberg et al., 2016), it remains to be investigated with regard to ToM.

Fifth, the generalizability and interpretability of the existing body of research related to the different constructs of ToM is limited as many different tasks are used, and it is often unclear which ToM construct is being measured. Therefore, it may give insight if a task battery is used, that assesses performance on different constructs of ToM, and controls for overlap between constructs. Furthermore, tasks may be developed which take differences in cognitive style (e.g. hyper- vs. hypomentalism) into account, as well as affect-driven biases (as may be relevant specifically in MDD).

Finally, as there is considerable symptomatic overlap between, and diversity within, affective and psychotic illnesses, is plausible that the presence or absence of certain symptoms within an individual bear a stronger relationship to ToM functioning than does diagnostic category. Moreover, preliminary research suggests that fundamental differences in mentalizing style may underlie symptomatic diversity between patients of the same diagnostic category, at least in SZ (Bliksted et al., 2018; Peyroux et al., 2019). Thus, a symptom-oriented approach, cutting across categorical boundaries to affective and psychotic disorders is advisable in future ToM research.

4.4. Concluding remarks

Taken together, deficits in ToM are present in patients diagnosed with psychiatric illnesses in the affective-psychotic spectrum (SZ, BD, or MDD) as well as in their respective spectrum disorders. The pattern we observed suggests that ToM deficits are most severe in SZ, and least severe in MDD. Deficits in BD are intermediate and are generally found to be significantly smaller than those observed in SZ. However, it is possible that during manic episodes, effect sizes for BD may approach those reported in patients with SZ.

Furthermore, in BD and SZ, and possibly in MDD, attenuated deficits are present in the remitted stages. In SZ and BD, the extended illness phenotype has been associated with impaired ToM, which may reflect some form of trait vulnerability to the development of psychiatric illness. As such, it is likely that ToM deficits in patients with these disorders consist of both a trait and a state component. This fits the somewhat mixed, but generally positive findings that poor ToM performance is associated with symptom severity across affective and psychotic disorders.

Interestingly, the observed gradient pattern suggests that ToM deficits scale with the level of risk and severity of the disorders. The largest ToM deficits are found in the most severely impaired groups (symptomatic patients with SZ, BD patients during a manic phase) and smaller deficits are present in groups with relatively fewer symptoms (patients with non-psychotic MDD, BD patients during a depressive phase, remitted SZ patients). Supporting this idea, groups at familial risk of SZ are more impaired on measures of ToM than those at familial risk of BD, and both groups perform intermediately to symptomatic patients and the healthy population. It is important to note that in patients with SZ, correlations between ToM deficits and the negative and disorganized symptom dimensions are more consistently found than correlations between ToM deficits and positive symptoms. Perhaps differences in effect size between SZ and the affective disorders can be attributed in part to the more frequent occurrence of negative and disorganized symptoms in the schizophrenia spectrum disorders.

To summarize, our findings suggest that variance in ToM performance can be explained by both the categorical as well as a dimensional approach. It appears that a loss of social cognitive faculties is both a trait marker and a state-dependent feature of severe mental illness in the psychosis-mood spectrum, and it is imperative that its role in the development and maintenance of psychotic and affective symptoms is investigated in more detail using a cross-disorder approach while taking into account different aspects of ToM within the patient groups. Although the general pattern suggested by our findings corroborates our hypothesis that deficits in ToM scale with the severity of psychotic symptoms, it is important to note that significant mentalizing deficits are also present in patients with non-psychotic affective disorders, and that these deficits appear to exceed those found in individuals at clinical high risk for psychosis. As such, it is likely that deviations in ToM are associated with factors other than psychosis severity; for example with the mood-congruent cognitive biases that are frequently observed in patients with affective disorders.

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None.

Declaration of Competing Interest

None.

Appendix I

Tables 1–4**– Overview of the reviews considered in this systematic review of secondary literature.** Note that not every review has a primary focus on ToM, and that we only considered between-group comparisons in ToM, associations of demographic and clinical variables with ToM capabilities (reported here only when the focus of the review is on associations rather than between-group comparisons) and comparisons between ToM subdomains within patients. Group size is reported for meta-analyses only and is reported for the clinical group(s). Tables are ordered so that meta-analysis are considered before systematic reviews and literature reviews, and articles investigating patient groups are considered before those in high-risk and first episode groups.

Clinical groups

HC = healthy controls.

Schizophrenia spectrum groups

SSD = schizophrenia spectrum disorders, *SZ* = schizophrenia, *aSZ* = acute/symptomatic schizophrenia, *rSZ* = remitted/asymptomatic schizophrenia, SZA = schizoaffective disorder, *FEP* = first episode psychosis, *cHR* = clinical high risk risk of psychosis, *DD* = delusional disorder, *SZT* = schizotypy, *SZfHR* = familial high risk for psychosis.

Bipolar groups

BD(-I/-II) = bipolar disorder (type I or II), *aBD* = acute/symptomatic bipolar disorder, *rBD* = remitted/euthymic bipolar disorder, *ssBD* = remitted bipolar disorder with subsyndromal symptoms, *BDfHR* = familial high risk for BD.

Depressive groups

MDD = major depressive disorder, *aMDD* = acute/symptomatic depression, *rMDD* = remitted/asymptomatic depression, *PDD* = persistent depressive disorder (chronic depression, dysthymic disorder, depressive personality disorder).

Individual ToM tasks

RMET = reading the mind in the eyes test, *HT* = hinting task, *FB* = false belief stores, *FB-seq* = false belief picture sequencing, *FP* = faux-pas, *SS* = strange stories.

Task domains

aToM = affective ToM, *cToM* = cognitive ToM, *veToM* = verbal ToM, *viToM* = visual ToM.

Associations

+ = impairments in ToM correlate with increases in this variable.
– = impairments in ToM correlate with decreases in this variable.
~ = no correlation of variable with ToM task performance.
+/~ = trend-level or suggestive evidence that ToM impairment correlates with increases in this variable.
–/~ = trend-level or suggestive evidence that ToM impairment correlates with decreases in this variable.

Effect sizes

d = Cohen's d, *g* = Hedge's g, == = no significant difference found between effect sizes.

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