Published in final edited form as:
Bipolar Disord. 2013 November ; 15(7): 723–740. doi:10.1111/bdi.12115.

Disturbances in reality testing as markers of risk in offspring of parents with bipolar disorder: a systematic review from a developmental psychopathology perspective

Angela J Narayan[a], **Timothy A Allen**[a], **Kathryn R Cullen**[b], and **Bonnie Klimes-Dougan**[c]
[a]Institute of Child Development, University of Minnesota, Twin Cities, Minneapolis, MN, USA
[b]Department of Psychiatry, University of Minnesota, Twin Cities, Minneapolis, MN, USA
[c]Department of Psychology, University of Minnesota, Twin Cities, Minneapolis, MN, USA

Abstract

Objectives—This comprehensive review examined the prevalence and progression of disturbances in reality testing (DRT), defined as psychotic symptoms, cognitive disruptions, and thought problems, in offspring of parents with bipolar disorder (O-BD). Our approach was grounded in a developmental psychopathology perspective and considered a broader phenotype of risk within the bipolar–schizophrenia spectrum as measured by categorical and dimensional assessments of DRT in high-risk youth.

Methods—Relevant studies were identified from numerous sources (e.g., PubMed, reference sections, and colleagues). Inclusion criteria were: (i) family risk studies published between 1975 and 2012 in which O-BD were contrasted with a comparison group (e.g., offspring of parents who had other psychiatric disorders or were healthy) on DRT outcomes and (ii) results reported for categorical or dimensional assessments of DRT (e.g., schizophrenia, psychotic symptoms, cluster A personality traits, or thought problems), yielding a total of 23 studies.

Results—Three key findings emerged: (i) categorical approaches of DRT in O-BD produced low incidence base rates and almost no evidence of significant differences in DRT between O-BD and comparison groups, whereas (ii) many studies using dimensional assessments of DRT yielded significant group differences in DRT. Furthermore, (iii) preliminary evidence from dimensional measures suggested that the developmental progression of DRT in O-BD might represent a prodrome of severe psychological impairment.

Conclusions—Preliminary but promising evidence suggests that DRT is a probable marker of risk for future impairment in O-BD. Methodological strengths and weaknesses, the psychometric properties of primary DRT constructs, and future directions for developmental and longitudinal research with O-BD are discussed.

Keywords

bipolar disorder; developmental pathways; family risk; psychosis; thought problems

Corresponding author: Angela J Narayan, Institute of Child Development, University of Minnesota, 51 East River Road, Minneapolis, MN 55455, USA, Fax: 612-624-6373, anarayan@umn.edu.

Disclosures: The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

Consistent with the developmental psychopathology concept of multifinality, defined as the potential for multiple outcomes from a common source of risk (1), there is strong evidence for many deleterious outcomes in children being born to and raised by a parent with bipolar disorder (2–4). As bipolar disorder is one of the most heritable types of mental illness (5, 6), the risk of this disorder is critically important to consider, given that 4–15% of offspring of parents with bipolar disorder (O-BD) will go on to develop bipolar disorder (7– 9). Yet, developing bipolar disorder represents only part of their risk profile for O-BD. Up to 40–60% of O-BD may develop moderate to severe forms of psychopathology during childhood and adolescence (3, 10–12).

Also consistent with the developmental psycho-pathology perspective is the importance of identifying the course and timing of deviations to atypical functioning from normative development (13, 14). For example, while there is mixed evidence regarding the extent to which O-BD experience significant psychopathology in early childhood, there is ample evidence that by adolescence many O-BD may suffer from a range of problems (10, 11, 15, 16). Indeed, many pressing questions linger about the etiological sources of the wide range of problems that manifest in those being born to and raised by a parent with bipolar disorder. Recent efforts are beginning to consider the broader array of outcomes in O-BD, including an increased prevalence of low-incident outcomes that involve disturbances in reality testing (DRT) (17).

This review is intended to sharpen current understanding of potential outcomes in O-BD by focusing on a less understood but potentially severe and debilitating outcome. Specifically, our focus is on the transmission of a broader spectrum of problems that include psychotic symptoms and other behavioral indicators suggestive of DRT (e.g., 18–21). We define DRT as an inclusive construct characterized by hallucinations, delusions, significant disruptions in cognition (e.g., loosening of associations, tangential thought patterns, magical thinking, and apophenia) and other manifestations of atypical behavior oddities or perseverations (17, 22). While DRT is most easily identified in schizophrenia-spectrum disorders and psychosis, these disturbances may also be observed in a broader range of psychiatric conditions (e.g., bipolar disorder with psychotic features, obsessive compulsive disorder, and dissociative disorder). DRT also includes prodromes for psychotic conditions (e.g., schizoid personality disorder) and dimensions more commonly distributed across the population [e.g., numbers of thought problem symptoms on the Child Behavior Checklist (CBCL) (23)].

DRT from a developmental psychopathology perspective

Researchers interested in understanding developmental discontinuities such as DRT must actively consider the normative processes from which these symptoms may arise (13, 14, 24). Early normative distortions in reality testing might best be understood by considering the intricate fantasy worlds that children create for themselves throughout the course of development. For example, in early childhood, imaginary companions and other forms of imaginary impersonation are normative (25–27). These aspects of pretend play have been associated with a number of important developmental adaptations including advanced theory of mind, sociability, and creativity (28–30), but under some conditions may also be associated with increases in dissociative thought, as well as the tendency to experience imaginary verbal experiences (31, 32). While the presence of such behavior is not in itself pathological, these associations do suggest that deviations in, or prolongations of, the normative developmental progression of reality testing may place one at increased risk for psychopathology (33).

Symptoms of psychosis and thought problems may represent the point at which reality testing becomes maladaptive and likely disrupts the path of normative development in

childhood and adolescence. Psychotic symptoms may interfere with the ability to master normative age-salient developmental tasks, such as coordinating emotional and behavioral regulation, creating a firm but flexible sense of self, forming meaningful interpersonal relationships, achieving symbolic thought and object relations, and successfully navigating tumultuous developmental transitions, such as puberty (4, 34–36). From a prognostic standpoint, psychotic symptoms or related aspects of DRT may be a prodrome of bipolar disorder (6, 37) or schizophrenia (38), signaling significant deviations from adaptive to atypical functioning. Thus, it is likely that psychotic symptoms not only reflect concurrent impairment but also predict fundamental changes for the worse. Consequently, regardless of which disorder DRT may foreshadow, these problems may elevate risk for severe impairment, portend a worsening course of illness, and increase morbidity (34, 39–41).

Characterizing the bipolar disorder–schizophrenia spectrum

Evidence documenting the transmission of DRT in O-BD would add to the literature that supports a phenotypic and genetic overlap between psychotic disorders (e.g., schizophrenia and schizoaffective disorder) and bipolar disorder. This overlap is conceptualized as the bipolar–schizophrenia spectrum. Historically, Kraepelin (42) dichotomized manic-depressive insanity (bipolar disorder) and dementia praecox (schizophrenia). However, despite unique properties of each disorder having been delineated (20, 21, 43), researchers investigating this overlap over the last decade have adopted a spectrum-based approach, which includes a broader phenotype and highlights similarities between bipolar disorder and schizophrenia in symptomatology, family risk, and genetic linkage (44–46).

Compelling support for common phenotypic features within this spectrum is evident. For example, approximately 58% of adults with bipolar disorder will experience at least one psychotic symptom during their lifetimes (18). Many individuals with either bipolar disorder or schizophrenia will carry diagnoses of both affective and psychotic illnesses at some point in their lives (46). Of children and adolescents presenting with first episodes of psychosis, approximately 16–18% are diagnosed with bipolar disorder (37, 47). Additionally, depending on the data source, the rates of comorbid psychosis in children with bipolar disorder range from 17 to 87.5% (6, 48, 49).

In addition to family risk studies, behavioral and molecular genetic studies with adults have provided additional support for the concept of the bipolar disorder–schizophrenia spectrum. Large cohort-based and genome-wide association studies have found shared risk factors for bipolar disorder and schizophrenia, including a family history of either disorder, childhood maladjustment, and stressful life events, and a small but significant genetic overlap (50, 51). Genetic overlap has also been documented in the increased risk for schizophrenia in biological relatives of individuals with bipolar disorder, offspring of parents who have bipolar disorder, and adopted individuals with a biological parent with bipolar disorder (19, 45, 52– 54). Furthermore, individuals with schizoaffective disorder, a potential intermediary between bipolar disorder and schizophrenia (e.g., 39, 44), are also more likely to have relatives with bipolar disorder or schizophrenia than schizoaffective disorder (45). Together, these studies provide strong evidence supporting co-aggregation of bipolar disorder and psychotic disorders and the existence of a unified spectrum.

Objective of the review

Despite these hallmark examples that provide evidence of shared features of bipolar disorder and schizophrenia, alternative methodologies are needed to consider risks within a developmental context. Most studies supporting a spectrum approach use categorically derived diagnostic instruments to assess adult relatives of probands with bipolar disorder who have already displayed the full clinical presentation of these low-incidence diagnoses

(52, 55). Although one might expect that higher risk for psychosis or other forms of DRT in first-degree relatives of adults with bipolar disorder would also extend to O-BD, schizophrenia and other psychotic (Axis I) or relevant personality disorders (Axis II) are not typically diagnosed before early adulthood. Thus, problems at the level of a full-threshold disorder may not be evident from diagnostic assessments conducted with O-BD in childhood and adolescence. Presumably, the current categorical, diagnostic approach may limit the understanding of the broader phenotype of DRT in O-BD, particularly in those who have yet to meet full criteria for relevant psychiatric disorders.

Consistent with Duffy et al.'s (56) recent call for the use of psychometrically sound, developmentally appropriate methodology, alternative approaches for detecting risk transmission should draw on aggregation methods based on a broader phenotype (e.g., considering psychosis as well as its prodrome). This would include dimensional approaches that enhance detection of earlier risk factors or relevant prodromes (e.g., by identifying clinically relevant symptoms of DRT) and yield valuable information on the origin or developmental progression of this broader spectrum. These approaches may also serve as relevant tests to further substantiate the unifying spectrum of bipolar disorder and schizophrenia.

Adopting a developmental psychopathology perspective, this review highlights promising findings and ongoing challenges in assessing DRT in youth at risk for bipolar disorder. The objectives of this review are to: (i) examine the prevalence of categorical diagnoses associated with DRT in O-BD (including assessments involving aggregation across a broader phenotype of risk) compared to control groups; (ii) compare and contrast whether DRT are more easily identified by clinically relevant symptoms from dimensional assessments rather than full-threshold diagnoses from categorical assessments; and (iii) examine the developmental progression of DRT to potential outcomes in O-BD.

Methods

Data collection and extraction

Similar to DelBello and Geller (10) and Duffy (57), we emphasize the need for controlled studies examining the scope of psychopathology and developmental progression of disorders in O-BD. Although longitudinal research is most germane to our purposes, owing to the underrepresentation of these studies in the current literature we also included cross-sectional findings to enhance our understanding of whether DRT are indeed common in children, how these symptoms may relate to developmental psychopathology, and what implications they may have for clinical assessment tools and developmental outcomes. Considering evidence spanning diverse developmental stages and methodologies may enhance our understanding of whether DRT are an area in need of continued inquiry.

This review was prepared in accordance with the Cochrane Collaboration Guidelines for Reporting Reviews (58). Prior to conducting our literature searches, we specified several inclusion and exclusion criteria. A central inclusionary criterion was to identify those at elevated risk for bipolar disorder, specifically O-BD. Due to the challenges of diagnosing bipolar disorder (56), we limited our review to offspring studies that diagnosed parental bipolar disorder by using a structured or semistructured psychiatric interview. Mothers and/or fathers could be diagnosed with either bipolar I (BDI-I) or bipolar II (BD-II) disorder. All studies considered in this review included a comparison group, which was typically a low-risk group of offspring of well parents (O-Well), but might also have been well offspring of parents with bipolar disorder (59), or a high-risk comparison group [e.g., offspring of parents with unipolar depression (60) or schizophrenia (61) or O-BD with different forms of

psychopathology (62)]. Ages of O-BD included in this review ranged from preschool (e.g., ages 2–5 years) through young adulthood (e.g., ages 20–25 years).

In terms of offspring inclusion criteria, the primary criterion was that some DRT-related outcome had to have been examined in O-BD, although DRT did not have to be the primary construct assessed. A broad array of theoretically relevant or empirically derived assessment tools was used to assess various aspects of DRT. Methodologies based on clinical interviews, self-reports, or parent reports were considered relevant for assessing categorical (primarily Axis I and Axis II diagnoses) as well as dimensional indices relevant to DRT outcomes.

Excluded from this review were studies that examined: (i) relatives of probands with bipolar disorder when the results failed to specify whether the relatives were offspring or parents; (ii) offspring of parents with affective disorders when the results failed to specify whether parents were diagnosed with bipolar disorder versus major depressive disorder (MDD); (iii) studies of O-BD that did not examine any outcome characterizing DRT; and (iv) multiple studies from the same laboratory that considered the same outcome variable. In that latter case, we identified the most recent or inclusive findings that were reported.

After establishing the inclusion and exclusion criteria, we identified relevant empirical studies that were published between 1975 and 2012 and written in English by: (i) searching the online databases Google Scholar, Pubmed, PsycInfo, and Medline for all key terms pertaining to the outcome criteria (e.g., *schizophrenia*, *schizoaffective*, *cluster A personality disorder*, *schizotypal*, *schizoid*, *paranoid*, *psychosis*, *psychotic symptoms*, and *thought problems*) within studies of O-BD, identified with key terms of parental criteria and family risk (e.g., *bipolar disorder*, *mania*, and *offspring*); (ii) examining references of published studies and reviews; and (iii) consulting experts in the field. Based on these criteria, 38 studies were selected, 15 of which were excluded, and 23 were reviewed. In accordance with disclosing risk bias of selective reporting within studies (58), five of the 15 excluded studies did not report DRT-related outcomes in O-BD or did not report whether they had indeed assessed DRT-related outcomes, although they used instruments that routinely assess DRT. Six of the 15 studies did not specify whether the parental affective diagnoses were MDD or BD; two of the studies did not specify whether the probands with bipolar disorder were offspring or adult relatives; and two of the studies were earlier reports by the same research team that used subsets of the same sample (63, 64). Thus, the most recently updated sample was utilized (65). Thirteen of these 23 studies examined categorical measures of DRT in O-BD (Table 1), and 13 studies examined dimensional ratings of DRT in O-BD (Table 2). Three studies used both dimensional and categorical methods; thus, they are presented in both tables.

Measures: types of categorical and dimensional assessments

The 13 categorical studies in this review incorporated several approaches used to estimate DRT psychopathology in O-BD (Table 1). These approaches included examining individual Axis I or II diagnoses, aggregating problems involving DRT or related diagnoses, and setting cut-off scores of dimensional measures. For example, data were reported at varying levels of aggregation. At times, more inclusive diagnostic classes (e.g., psychosis, schizophrenia-spectrum, or cluster A disorders) or cutoffs for clinical levels of symptoms were considered (17), while at other times the data reported were based on criteria for a specific diagnosis. Several Axis I disorders were considered centrally relevant to DRT (e.g., schizophrenia, schizophreniform disorder, psychotic disorder not otherwise specified, and schizoaffective disorder). Axis II cluster A personality disorders (i.e., paranoid, schizoid, and schizotypal) also were included as they may reflect severe forms of DRT and have been found to represent prodromes for psychotic disorders (38).

Axis I disorders were typically assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (e.g., based on the current version, DSM-IV-TR or the DSM-IV or DSM-III for older studies) within the contexts of semistructured or structured diagnostic interviews by trained clinicians. The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (66) was the primary diagnostic tool used for assessing Axis I disorders, with different research teams often using different K-SADS versions [K-SADS–Present and Lifetime Version (K-SADS-PL) (67) and Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (68)]. Other diagnostic measures included the Diagnostic Interview for Children and Adolescents–Child (DICA) and Parent (DICA-P) versions (69) and comprehensive assessments of psychotic disorders in adults, such as the Structured Clinical Interview for the DSM-IV (SCID) (70). Approaches to evaluate Axis II disorders were quite varied in the studies reviewed here, with only occasional reliance on structured or semistructured diagnostic interviews (e.g., 71), such as the SCID-II (72) and empirically derived self-report scales [Schedule for Nonadaptive and Adaptive Personality (SNAP) (73)]. Additionally, some Axis II diagnoses were based on clinical impressions (e.g., 65).

The most consistently used dimensional approach, utilized by eight of the studies listed in Table 2 (17, 62, 74–79) to evaluate DRT, was to examine raw or *T*-scores from the Thought Problems (TP) scale from the CBCL, Youth Self-Report (YSR), Young Adult Self-Report (YASR), Young Adult Behavior Checklist (YABCL), and Teacher-Report Form (TRF) (23, 80–82). The Achenbach scales are empirically derived from factor analytic techniques and have demonstrated sound internal consistency (23, 82) and test–retest reliability (e.g., r = 0.74 over a two-week interval) (83). Parent-reported (CBCL) and teacher-reported (TRF) TP include seven items encompassing hallucinatory or delusional behavior (‘*Hears sounds or voices that aren't there*’ and ‘*Sees things that aren't there*’), atypical behavior (‘*Strange ideas*’, ‘*Strange behavior*’, and ‘*Stares blankly*’) and perseveratory behavior (‘*Can't* get his/her mind off certain thoughts, *obsessions*’ and ‘*Repeats acts over and over*’). Self-report scales substitute ‘*stares blankly*’ for ‘*stores up things*’. Advantages of the TP scales are the availability of normative data and translations for this measure in a number of languages. In one study, the Children's Psychiatric Rating Scale (CPRS) (84) was used. In addition, instruments used for categorical purposes, such as diagnostic interviews, were in some cases used dimensionally to evaluate the number of DRT or psychotic systems endorsed by respondents.

Results

Categorical approaches for evaluating DRT in O-BD

Table 1 presents the 13 reviewed studies that reported rates and prevalences of specific Axis I and Axis II disorders that reflected DRT. Of these studies, eight reported that they conducted tests to analyze whether significant group differences were present (17, 65, 71, 85–89). These results generally revealed that Axis I DRT problems in O-BD were largely consistent with the low base rates of schizophrenia and other psychotic disorders in clinical samples and population base rates (38, 52). O-BD showed evidence of these problems at only slightly higher rates than the incidence expected in the general population, such as 1.7% (one of 60) to 3.5% (five of 141) of O-BD with schizoaffective disorder (65, 85) and 1.5% (two of 134) of O-BD with schizophrenia (90), all compared to 0% of O-Well. Even with relatively larger high-risk samples, some studies in Table 1 yielded non-significant group differences in Axis I or cluster A disorders in O-BD (71, 85). Notably, this interpretation must be qualified because many studies only reported descriptive information rather than tests of significant group differences (60, 61, 90, 91); however, in most cases the reported percentages suggested that group differences would likely not be significant.

Overall, these observations suggest that categorical approaches may reflect a low prevalence of these disorders, even in high-risk youth.

Aggregation of problems (e.g., across broader domains of DRT or across time) should optimize detection of group differences. Indeed, the highest rates of DRT were found in an early study by Akiskal et al. (92). Using a more inclusive dichotomous index, they reported evidence of 'bizarre behavior or psychotic proportions' in 16.2% (11 of 68) of O-BD compared to 0% of O-Well. Similarly, another research group with a much smaller sample found that 11.1% (two of 18) of O-BD were assessed as psychotic using a much smaller sample (however, comparisons to O-Well were not reported) (86). In both of these studies, the diagnoses were conceptualized as predominantly affective, including psychotic mania and psychotic depression, and may be suggestive of a higher incidence of affective psychosis in O-BD.

In Table 1, we also considered whether Axis II disorders relevant to DRT would be more highly represented in O-BD than in comparison groups. Of the seven studies from Table 1 that assessed cluster A personality disorder diagnoses (60, 61, 65, 71, 86, 87, 91), two studies showed evidence of elevations of these disorders in O-BD. For example, one study found evidence for schizotypal personality disorder in O-BD compared to O-Well, although specific numbers of individuals who had this disorder were not reported (87). In another laboratory, 8.3% (five of 60) of O-BD of lithium-nonresponsive parents had cluster A personality disorders compared to 0% of O-Well (and 0% of lithium-responsive parents) (65).

Finally, one study categorized DRT using cutoffs rather than diagnoses (17) by using clinically significant ($T \geq 70$) thresholds for TP rated with the CBCL (23). Using a prospective longitudinal design, this study found that 14.6% (seven of 48) of O-BD had clinically significant levels of TP during at least one of four assessments (spanning ages two to 17 years), which was significantly more than O-MDD (7.1%; six of 84) and O-Well (0%; zero of 60).

Dimensional approaches for evaluating DRT in O-BD

Dimensional approaches were examined as they may be better suited to capture more clinically relevant symptoms of DRT, promote the understanding of both continuities and discontinuities of functioning, and elucidate the gradual developmental deviation that may lead an individual down a pathway to full-blown psychopathology (93). Results from Table 2 indicate that dimensionally rated measures more clearly illuminated significant differences in DRT between O-BD and comparison groups because they highlighted problems at the level of the symptom rather than the diagnosis. For example, two studies reported elevations in TP for O-BD as compared to population norms (74, 75). An additional five of the 13 studies examined elevations in TP symptoms based exclusively on the CBCL and generally documented that they were significantly higher in O-BD compared to O-Well (17, 76–79).

It is also possible that the level of DRT differs in O-BD with BD diagnoses and O-BD who have not yet developed BD but are at risk for it. Indeed, TP were increased in O-BD diagnosed with BD compared to O-BD at risk for BD and O-Well, but this increase was not evident when comparing O-BD at risk for BD versus O-Well (76, 77). This pattern of findings may be partially due to the fact that the TP scale only contains seven items and may represent a more global impairment associated with DRT. Additional dimensional approaches that consider more targeted perceptual distortions are critically important to consider.

Alternative dimensional methodologies also illuminated elevations in DRT in O-BD compared to control groups. One study reported that 5.7% (eight of 141) of O-BD had psychotic symptoms derived from structured interviews, compared to 0% of O-Well (85). Similarly, another study that used a within-groups design without a healthy comparison group reported significantly higher mean scores in the psychotic cluster of the CPRS in O-BD with psychiatric diagnoses than in well O-BD (59). Finally, a longitudinal study that utilized psychiatric and healthy offspring comparison groups found that O-BD were significantly more likely than O-MDD or O-Well to display symptoms of cluster A personality disorders (schizotypal and paranoid) (71). Together, these findings provide preliminary but promising evidence that symptom elevations rather than categorical diagnoses may provide more clinically relevant information about DRT in O-BD. These dimensional approaches also highlight the need to parse O-BD into youth with BD diagnoses and youth at risk for bipolar disorder when examining DRT and associated impairments. Likewise, dimensional elevations must be examined across childhood and adolescence.

Developmental considerations for DRT

An important consideration is whether the reviewed studies are developmentally informative, with regard to (i) what developmental patterns of DRT are evident in O-BD and (ii) whether these perturbations of early development portend impaired functioning for O-BD compared to low or high-risk groups. Although many of the dimensional studies were cross-sectional and included a wide range of ages (e.g., 62, 75–78, 94), making it difficult to characterize DRT in specific developmental periods, an imperative consideration also is the developmental window being assessed. Ideally, elevations in DRT should be examined at developmentally relevant assessment points, such as during age-salient developmental tasks, developmental transitions or points in development when pathological conditions associated with DRT emerge (34–36). Reliance on longitudinal methodology, which is optimal yet rare, also has unique advantages in assessing within-person changes over time.

The following sections highlight the issues of developmentally relevant time periods and assessment tools, as sole reliance on diagnostic criteria creates a number of potential barriers for advancing understanding of low-incidence problems across development. Low base rates for many aspects of DRT make it unlikely that group differences in general will be found via the use of categorical assessment tools and even less likely that children will be identified using DSM-based instruments as they may be too young to display obvious signs of, and meet criteria for, low-incidence DRT disorders (15, 61, 90). Some of the current studies highlighted important differences in Axis II problems, such as cluster A personality disorders, in O-BD (e.g., 65). However, by definition personality disorders are typically not diagnosed before age 18 years, when personality traits are considered to become stable (38). Consequently, developmental patterns addressed in this section are almost exclusively based on dimensional assessments or, at the very least, the use of more liberal methods of dichotomizing symptoms by including broader assessments and/or subclinical symptoms.

Developmental course of DRT—The emergence and course of DRT in O-BD are relevant for understanding risk trajectories and informing clinical practice. One approach has been to consider a very narrow developmental window. For example, in a cross-sectional study, Reichart et al. (74) reported significantly self-reported TP in O-BD compared to normative samples of children aged 12–13 years. Another approach highlighted these patterns longitudinally. Klimes-Dougan et al. (17, 79) considered assessments at early childhood, middle childhood, early adolescence, middle adolescence, and early adulthood. Graphs of within-individual changes suggested that O-BD diverged from O-Well in emergence of TP between middle childhood and adolescence (depending on the severity of

TP considered). Furthermore, while emergence of TP only occasionally showed between-group differences for any one developmental stage, cumulative evidence across time yielded important results. Over 15 years and five assessment waves, there were significant differences in growth curve trajectories illustrated by 'survival analyses' [(97) e.g., having a TP was considered a failure to 'survive'], and persistence of TP across time (i.e., at least one TP symptom endorsed during at least two time periods) in O-BD as compared to O-Well. One of the studies by Klimes-Dougan et al. (17) illustrates a hybrid approach by using a dimensional scale categorically to examine various cutoffs (e.g., absence versus presence of a TP symptom or persistence versus no persistence of any symptom, subclinical symptom, or clinical-level symptom) as dichotomous points at which DRT levels are differentiated between risk groups.

Developmental markers for psychopathology—An additional developmental question that warrants attention is whether aspects of DRT represent markers, pre-conditions, or prodromes of impairment in O-BD before a psychological disorder fully emerges. In the group of studies listed in Table 1, the presence of psychotic or cluster A diagnoses in O-BD may represent well-formed psychological disorders (46); however, they do not provide information on developmental markers of risk. Conversely, studies listed in Table 2 that indicate elevations in TP in O-BD who have not yet developed bipolar disorder may provide tentative evidence for prodromes of psychopathology. One such study (17) assessed TP at four points in development (preschool through adolescence) in O-BD, O-MDD, and O-Well to predict psychopathology and general functioning in young adulthood. The persistence of TP from the CBCL was a significant predictor of internalizing and externalizing problems and poorer functioning in young adulthood [Global Assessment of Functioning (GAF) (95)]. Additionally, maternal-reported TP through adolescence predicted (at a trend level) young adult self-reported TP. Overall limitations of power hindered the ability to robustly predict youths' diagnoses, although TP predicted (at an almost marginally significant level, $p = 0.105$) a bipolar diagnosis in young adulthood for the whole sample.

Of note, other studies on DRT in non-O-BD samples have similarly noted the importance of considering the developmental course of DRT. While approximately 75 to 90% of developmental psychotic experiences are transitory, these problems are concerning when they persist (96). Longitudinal epidemiological studies noted poor prognoses for a portion of youth who displayed psychotic symptoms early in life. For example, 25% of 11-year-olds with psychotic experiences developed schizophreniform disorder by age 26 years (98). In their review of the existing literature, Van Os et al. (96) proposed that more severe psychotic symptoms were associated with increased exposure to environmental risk factors such as trauma, cannabis use, and urbanicity as well as underlying genetic factors. These issues warrant further attention in the field more generally as well as within the subgroup of O-BD.

Discussion

This review adopted a developmental psychopathology perspective to synthesize existing research on DRT in O-BD. We sought to determine whether aggregation of risk for psychopathology in O-BD across a broader phenotype, including the bipolar–schizophrenia spectrum, would provide insight into DRT in O-BD. These questions were addressed by reviewing the extant literature on categorical and dimensional assessments of this broader phenotype of DRT in O-BD. We also aimed to determine whether the current methodologies provided insight into the developmental progression of DRT in O-BD. The current findings revealed a number of patterns corresponding to each of these aims.

Findings on DRT from categorical and dimensional approaches

The conclusions that can be drawn from categorical indices of DRT are mixed. We found that, typically, studies (e.g., 61, 90, 91) examining DRT through categorical diagnoses of schizophrenia-spectrum disorders, schizoaffective disorder, psychotic disorders, or cluster A personality disorders yielded findings that either were mostly consistent with low base rates of these disorders in the general population (38, 52), or indicated nonsignificant group differences between O-BD and children of O-Well or children of parents with other psychiatric diagnoses (71, 85, 86, 88). Categorical aggregation of psychopathology with DRT features, such as by generating diagnoses of 'affective psychosis' (92) or aggregating all individuals who were 'psychotic' (86), yielded higher rates of DRT in O-BD. However, regarding our developmental aims, categorical indices did not reveal optimal information on a developmental progression or prodrome of broader risk in O-BD.

Considering dimensional indices of DRT may provide an alternative approach that is more sensitive to understanding the disturbances that O-BD experience. The most striking findings from Table 2 indicated that DRT elevations in O-BD might be more closely identified by dimensional ratings of TP. Many studies found that O-BD had higher TP compared to O-Well, particularly for parent-reported TP from the CBCL (17, 76–79). These findings suggest that O-BD may indeed be at heightened risk for DRT, and the construct of TP may be one measure that can begin to identify the nature of this risk.

Additional support for the utility of assessing TP includes good construct validity of TP in children with mania versus ADHD (99–101) and psychosis versus ADHD (102). However, limitations of the TP construct involve the range of items that encompass these scales. Some of the most frequently endorsed items pertain to thoughts or behaviors that may be more obsessional or compulsive than psychotic in nature; thus, reliance on alternative dimensional measures of psychotic symptoms is also recommended. For example, it may be useful for research investigators or clinicians to examine symptom counts endorsed within the context of diagnostic assessments as a way to identify these low-incidence problems.

Developmental psychopathology

The current findings also have implications for developmental psychopathology research on DRT. Studies listed in Table 2 that best inform the developmental progression of DRT are those with longitudinal designs. For example, tentative evidence suggests that O-BD may show significantly more continuity and discontinuity of TP and cluster A symptoms across development, as well as variations in symptom elevations at different developmental periods, compared to psychiatric and healthy comparison groups (17, 71, 79). DRT may signal a prodrome of impairment and portend psychiatric illness, as TP in childhood and adolescence may be associated with a guarded prognosis in adulthood (17). While cross-sectional studies may address whether TP are concurrently associated with, or markers for, psychopathology, longitudinal studies provide a better opportunity to predict impairments in functioning over time. Much more prospective longitudinal research is needed to clarify and sharpen these developmental trajectories. Additionally, research on DRT could optimally begin assessments as early in development as possible and extend alternative but promising measures of DRT, such as open-ended story-telling paradigms (103), to O-BD preschoolers.

More research also is needed to understand the degree to which DRT deviates from normative development, which spans adaptation to impairment. For example, one interpretation of our results may be that O-BD have a greater tendency to exhibit adaptive characteristics of accelerated thought processes, such as divergent thinking or heightened creativity, rather than distorted or problematic thought. There is evidence that increased creativity may be evident in individuals with BD (e.g., 104, 105) and psychosis (106), and

some research indicates that these thought processes may be attributed to heightened productivity during hypomanic episodes (107, 108). These ideas have been applied to research on normative versus developmental deviations in personality functioning. For instance, factor analytic research by DeYoung and colleagues (109) suggested that both adaptive and maladaptive features of DRT may lie on a broader continuum defined by the Big Five personality trait Openness (110). Consistent with normative forms of DRT, traits like creativity, imagination, and aesthetic appreciation are core features of Openness. However, at the extreme dimensions of Openness, more maladaptive features begin to emerge, including apophenia (109) and the tendency to experience distorted perceptions. Factor analysis has also shown that these atypical features of Openness exhibit secondary associations with negative affect, supporting the idea that DRT may play a central role in certain forms of psychopathology (109) and, plausibly, the schizophrenia prodrome.

Mechanisms of transmission of DRT in development—An understanding of how DRT are passed down the generations of descendants with bipolar disorder remains elusive. Agreement on the nature of genetic loading and parental risk transmission of bipolar disorder itself is still unresolved, with some studies reporting that risk trajectories may be more virulent in youth with mothers with bipolar disorder (111), while others report that the transmission of bipolar disorder may be stronger for youth with affected fathers (112). Although this preliminary evidence from dimensional studies suggests that DRT may be transmitted more broadly than the full syndrome of bipolar disorder, the pattern of transmission of DRT may be difficult to decipher. To address these issues, future research with larger samples that examines DRT in O-BD with psychotic features versus those without psychotic features would sharpen understanding of the transmission patterns of DRT. Plausibly, DRT is more often transmitted to offspring when the parent has bipolar disorder with psychotic features.

Although we found almost no evidence of studies that were able to examine DRT in O-BD whose parents did or did not have psychotic features, two important differences in parent populations emerged. First, the reviewed studies varied in the extent to which parents with bipolar disorder were recruited from inpatient versus outpatient psychiatric settings; the categorical studies were almost evenly split in use of inpatient versus outpatient groups, while the dimensional studies almost completely drew from outpatient settings. Second, the reviewed studies also varied in whether parents with BD-II, in addition to BD-I, were included in the O-BD groups. Again, the categorical studies were more evenly split (although many did not specify), while the dimensional studies more commonly included BD-II. Taken together, these findings imply that the categorical studies may have been more likely to sample parents who were potentially more impaired. Furthermore, these categorical studies may have been well suited to identify O-BD impairment had they evaluated clinical symptoms rather than categorical diagnoses.

Given that research to date continues to emphasize the dynamic transactions between parental psychopathology and impairment and child psychopathology and impairment (2, 113, 114), future research needs to elucidate family mechanisms that account for risk in O-BD. Recent research has highlighted that the level of impairment in O-BD stems not only from parental mental health history but also from parental concurrent impairment, including parental negativity (2, 115). Research studies that parse out these questions are challenging and may require study designs that examine reared-apart twins, second-degree relatives (e.g. nieces, nephews, and grandchildren) of BD probands, or at-risk children with stabilized parents.

Bipolar–schizophrenia spectrum from a developmental perspective—Drawing primarily from family risk methodology, findings from Table 2 provide support for the

notion that O-BD are at risk for a broader phenotype of psychopathology in the bipolar–schizophrenia spectrum, characterized by DRT. These findings are tentative, given that many samples are cross-sectional and small in size. More studies are needed to target the developmental progression of DRT within the bipolar–schizophrenia spectrum conceptualization. While a multitude of studies have extensively examined transmission patterns of bipolar disorder in O-BD families (10, 57, 113) as well as risk for psychosis in children with bipolar disorder (6, 37, 47, 48), more research is needed to merge these lines of research. Such efforts should include examining DRT in addition to affective psychopathology in O-BD, and clarifying parental psychiatric status such as inpatient history, psychotic symptoms, and the BD-I/BD-II distinction.

Methodological issues that warrant continued consideration

Specificity of findings—It is important to consider if elevations of TP are specific to O-BD. Although many of the reviewed studies included a low-risk comparison group, high-risk comparison groups are also important for determining if DRT represents a specific risk for O-BD or a more general risk associated with a range of unfavorable conditions. A growing body of relevant research is available pertaining to this issue. Six studies listed in Table 2 included a parent psychiatric comparison group (e.g., O-MDD). Four of these studies reported that O-BD had the highest rates of TP (17, 71, 78, 79), at least on the CBCL, but two studies (15, 94) reported no differences or mixed results. These inconsistencies may be due to the different types of DRT presentations (e.g., subclinical thought problems, clinically significant psychotic symptoms, or communication patterns) across high-risk groups (94) and the unique developmental stage assessed (15). Therefore, future investigation on the issue of specificity of DRT in O-BD and high- and low-risk comparison groups should carefully consider multiple developmental stages and try to capture a wider range of DRT.

A second specificity issue is whether DRT reflects a specific type of psychopathology or a proxy for broader impairment. This is a challenge because DRT is distributed across the population at low rates (23, 116, 117). Generally, elevations on the TP scales may indicate greater overall, but less well-defined psychopathology (including aspects of obsessions and compulsions) (118). Moreover, O-BD with higher rates of psychopathology may have more TP (e.g., 62) suggesting elevations in TP may simply represent a secondary marker of broad impairment. One way to indirectly address this question is to evaluate if the developmental trajectories across many problems (i.e., DRT and other psychopathology) present in O-BD are similar or different. For example, preliminary evidence suggests different risk patterns for TP and another low-incident problem in O-BD, suicide risk (119). Ideally, efforts to evaluate the specificity of TP would control for other problems, but to date this approach has not been utilized, primarily because of limited power.

A third specificity issue pertains to predictive utility. Given the challenges associated with longitudinal measures of DRT, research is at the most preliminary stages of addressing these issues and is obscured by reports that approximately 75–90% of DRT are transitory and disappear over time (96). What is becoming evident is that a persistent course of DRT across development portends poor outcomes (17). Broadly, more research is needed to sharpen understanding of the multi-finite forms of psychopathology stemming from DRT (1, 4, 34).

Strengths and limitations of categorical versus dimensional approaches—Both categorical and dimensional approaches for measuring DRT have relative strengths and weaknesses. Advantages of using existing categorical measures include reliance on established criteria based on the DSM (e.g., diagnostic criteria) or other empirically derived criteria (e.g., clinical-level cut offs), standards for conducting structured and semistructured

clinical interviews, evidence of high inter-rater reliability, and aggregation approaches of multi-informant reports from parent and child interviewees (e.g., 3, 60, 87). Weaknesses include resources needed to train or employ interviewers and lengthy blocks of participants' time needed to complete interviews. The most striking weakness relevant to the body of literature reviewed here is that categorical measures may yield less clinically relevant information about DRT than dimensional assessments. However, this weakness could be ameliorated by increased attention to symptom counts (e.g., of psychotic symptoms) that are endorsed within categorical assessments.

Strengths of the dimensional approach include an ability to identify low-incidence, maladaptive behaviors, such as DRT, and to do so in samples with (i) smaller cell sizes between comparison groups; (ii) offspring at risk for psychopathology but who have yet to display diagnostic criteria for disorders; and (iii) measurement across time via limited burden of time or cost to participants or investigators. However, given that elevations on some of these scales may be broadly associated with a host of psychological problems (118), it may be useful to consider more narrowly defined constructs such as psychotic symptoms or apophenia. Additionally, moving forward it will be important to continue to validate reports of DRT with observable, atypical aberrant behaviors.

Issues of diverse and multiple informants—In diagnostic studies of children and adolescents, assessments of psychopathology typically include both parent and child perspectives, whereas for older adolescents and young adults, diagnosis is typically based on self-reports. Consensus between informants is not always evident; many studies listed in Table 2 relied on the parent or the child report only. In one of the few studies that included child, parent, and teacher informants in the assessment of 6–18-year-old participants, maternal reports of TP were elevated for O-BD versus O-Well, but self-and teacher-reports were not (78). In contrast, in a sample of 12–13-year-olds, O-BD reported significantly more TP than O-Well, but maternal and teacher reports did not differ (74). Furthermore, the gender of the child participant may differentially influence these biases. Wals et al. (75) found that mothers with bipolar disorder reported greater rates of TP in their 12–21-year-old sons, but these O-BD boys self-reported significantly lower TP than the sons of well mothers. These findings illustrate how, across age and gender, parents, teachers, and offspring may perceive and report TP differently.

Given that maternal report was predominantly utilized in many of these studies, it is also critical to consider the potential effects of parents' psychopathology on distorted perceptions of offspring behavior and functioning. There is ongoing controversy about the validity of depressed mothers as accurate reporters (e.g., 120–122). While numerous studies document the effects of depression on maternal reports in women with unipolar depression, less information is available on potential biases of mothers with bipolar disorder. However, Klimes-Dougan (123) found that mothers with bipolar disorder tended to overestimate their children's symptoms (in that case, suicidal symptoms), as compared both to children's self-reports and to the reports of mothers with unipolar depression, who tended to underestimate their children's symptoms. Moreover, the findings of studies that have compared the reports of children's behaviors from depressed mothers versus nondepressed fathers versus offspring themselves also tend to be mixed (75, 124). Despite these potential biases, mothers are critical sources of information and there is evidence of modest associations regarding child and parent reports of O-BD symptoms (125). Taken together, findings to date indicate that parental reports of children may range in accuracy (120), likely in part due to parents' disease state. It is recommended that future studies continue to aggregate multiple sources of information to elucidate the developmental progression and presentation of DRT.

Conclusions

In summary, this review aggregated and synthesized research on the presentation of DRT in O-BD via parsing and examining categorical and dimensional approaches and the developmental progression of the DRT construct. Broadly speaking, research to date provides preliminary but promising evidence that dimensional measures of DRT may provide more clinically relevant symptoms regarding the broader phenotype of risk in O-BD. Moving forward, a sharper and deeper focus on the developmental progression of risk in O-BD, including typical and aberrant forms of DRT in young children, would enhance empirical research and clinical practice with these high-risk youth. Dimensional measures of DRT are highly compatible with the developmental perspective; not only are they consistent with the next wave of psychiatric disorder classification (126), but they provide the means to identify a graded spectrum of risk and pathways to psychiatric illness over time in at-risk children (17, 56, 113).

Clinical adaptation of DRT assessment tools for use in treatment settings would provide clinicians with information about a broader spectrum of risks facing O-BD. Given the potentially complex and intertwining course of many psychiatric illnesses in which DRT may be present (118, 127), it is critical that clinicians use dimensional measures to examine subclinical elevations of risk that may be markers or prodromes of psychopathology or, conversely, begin to examine the total number of symptoms endorsed within categorical diagnoses. Promising directions for future research to address these gaps could include utilizing dimensional scales to examine psychotic processes and thought problems across development, diverse forms of offspring risk groups, and transactional levels of family influence.

Acknowledgments

Preparation of this manuscript was supported by a predoctoral traineeship from the National Institute of Mental Health (NIMH; 5T32MH015755) and a graduate school fellowship from the University of Minnesota awarded to AN. Any opinions, conclusions, or recommendations expressed in this paper are those of the authors and do not necessarily reflect the views of the NIMH or the University of Minnesota.

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Bipolar Disord. Author manuscript; available in PMC 2014 November 01.

Table 1

Studies using categorical measures of disturbances in reality testing (DRT) in offspring of parents with bipolar disorder (O-BD)

Study	Measure	N	Age	Comparison group(s)	Type of study	Summary of findings
Akdemir and Gökler 2008 (88)	K-SADS-PL	69	6–17 years	O-BD (n = 36) O-Well (n = 33)	Cross-sectional	2.8% (1/36) of O-BD had a psychotic disorder compared to 0% of O-Well, but this difference was not statistically significant
Akiskalet al. 1985(92)	Washington University/ Feighner Criteria similar to DSM-III	136	6–24 years	O-BD (n = 68) O-Well (n = 68)	Cross-sectional	16.2% (11/68) of O-BD patients showed ‘bizarre behavior of psychotic proportions’ (including psychotic mania and psychotic depression) and 11.8% (8/68) presented with acute versus intermittent affective onset with psychosis compared to 0% of O-Well Did not report tests of significant differences
Cullenet al. 2011 (71)[a]	SCID-II	167	4, 7, 11, 15, and 22 years of age at Times 1–5	O-BD (n = 42) O-MDD (n = 73) O-Well (n = 52)	Longitudinal	There were no significant differences between offspring risk groups for cluster A personality disorders
Duffy et al. 2007 (65)	K-SADS-PL	188	8–25 years	O-BD of LR parents (n = 67) O-BD of LNR parents (n = 60) O-Well (n = 61)	Prospective over 0–9 years	8.3% (5/60) of O-BD-LNR parents had significantly more pre-psychotic conditions such as cluster A trait disorders compared to 1.5% (1/67) of O-BD-LR and 0% of O-Well; and 1.7% (1/60) of O-BD-LNR had schizoaffective disorder or psychosis-NOS compared to 0% of O-BD-LR and 0% of O-Well (not significant)
Erlenmeyer-Kimling et al. 1995(86)	SADS-L RDC	188	≥18 years	O-affective (O-Aff; n = 41 O-BD or O-MDD O-SZ (n = 54) O-Well (n = 93)	Cross-sectional	11.1% (2/18) of O-BD developed psychosis, and in both cases, the parents had BD with psychosis Did not report psychosis in comparison groups No significant group differences between O-Aff and O-Well on cluster A personality disorders
Erlenmeyer-Kimling et al. 1997(89)	SADS-L RDC	287	≥18 years	O-Aff (n = 67; did not specify BD versus MDD) O-SZ (n = 84) O-Well (n = 136)	Cross-sectional	9.0% (9/67) of O-Aff had schizoaffective disorder, SZ type compared to 1.2% (1/84) of O-SZ and 0% of O-Well; this was only significantly different compared to O-Well, but they reported that O-Aff unipolar versus BD distinction did not significantly affect these results
Grigoroui-Serbănescu et al. 1989(87)	K-SADS-E	144	10–17 years	O-BD (n = 72) O-Well (n = 72)	Cross-sectional	12.5% (9/72) of O-BD had four different personality disorders, one of which was cluster A schizotypal personality disorder, compared to 2.8% (2/72) of O-Well; this difference was reported to be significant
Kashaniet al. 1985(60)	DICA DICA-P	50	7–17 years	O-BD (n = 9) O-MDD (n = 41)	Cross-sectional	0% of O-BD had schizoid personality disorder compared to 7.3% (3/41) of O-MDD

Study	Measure	N	Age	Comparison group(s)	Type of study	Summary of findings
						Did not report tests of significant differences
Klimes-Dougan et al., in press (17)[a]	CBCL	192	4, 7, 11, 15, and 22 years of age at Times 1–5	O-BD (n = 48) O-MDD (n = 84) O-Well (n = 60)	Longitudinal	14.6% (7/48) of O-BD had significantly more clinical levels (T ≥ 70) of thought problems at two or more time points, compared to 7.1% (6/84) of O-MDD and 0% of O-Well
Maziade et al. 2008(61)	K-SADS SCID	54	7–22 years	O-BD (n = 26) O-SZ (n = 28)	Cross-sectional	0% of O-BD had diagnoses of psychotic disorders (e.g., SZ) or cluster A personality disorders
						Did not report tests of significant differences
Nurnberger et al. 2012(85)[a]	DIGS WASH-U-KSADS	232	12–21 years	O-BD (n = 141) O-Well (n = 91)	Cross-sectional	3.5% (5/141) of O-BD had a psychosis-type disorder (schizoaffective disorder) and 5.7% (8/141) of O-BD had any psychotic symptom, compared to 0% of O-Well, but these differences were not significant
Schubert and McNeil 2003(91)	SCID	166	22 years	O-BD (n = 16) O-Other high risk (n = 59) O-Well(n = 91)	Cross-sectional	0% of O-BD had psychosis and 6.3% (1/16) offspring had a cluster A disorder (did not distinguish whether this was an O-BD or an O-MDD)
						Did not report tests of significance differences
Weintraub 1987(90)	SADS SCID	544	'School-age'	O-BD(n = 134) O-SZ (n = 80) O-MDD(n = 154) O-Well(n = 176)	Prospective over 3 years	1.5% (2/134) of O-BD had SZ when followed up at age 18 compared to 2/5% (2/80) of O-SZ, 10% (1/80) of O-MDD, and 0% of O-Well
						Did not report tests of significant differences

CBCL = Child Behavior Checklist; DICA = Diagnostic Interview for Children and Adolescents (P = Parent version); DIGS = Diagnostic Interview for Genetic Studies; K-SADS = The Kiddie Schedule for Affective Disorders and Schizophrenia (PL = Present and Lifetime version; WASH-U = Washington University version; E = Epidemiological version); NOS = not otherwise specified; O-Aff = offspring of a parent with an affective disorder (MDD or BD); O-BD-LNR = offspring of a parent with a nonpositive response to lithium; O-BD-LR = offspring of a parent with BD with a positive response to lithium; O-BD = offspring of a parent with bipolar disorder (BD); O-MDD = offspring of a parent with major depressive disorder (MDD); O-Other = offspring of a parent with a psychiatric disorder other than bipolar disorder; O-SZ = offspring of a parent with schizophrenia; O-Well = offspring of psychiatrically well parents; RDC = Research Diagnostic Criteria; SADS = Schedule for Affective Disorders and Schizophrenia (L = Lifetime version); SCID = Structured Clinical Interview for the DSM-IV.

[a] Also reviewed in Table 2.

Table 2

Studies using dimensional measures of disturbances in reality testing (DRT) in offspring of parents with bipolar disorder (O-BD)

Study	Measure	N	Age	Comparison group(s)	Type of study	Summary of findings
Birmaher et al. 2010(15)	K-SADS-PL	223	2–5 years	O-BD (n = 121) O-Other or Well (n = 102)	Cross-sectional	No significant group differences emerged in number of psychotic symptoms between O-BD and O-Other/Well
Cullen et al. 2011 (71)[a]	SNAP	167	4, 7, 11, 15, and 22 years of age at Times 1–5	O-BD (n = 42) O-MDD (n = 73) O-Well (n = 52)	Longitudinal	O-BD were significantly more likely to develop symptoms of cluster A personality disorders (schizotypal and paranoid) than O-MDD and O-Well at Time 4
Dienes et al. 2002 (62)	CBCL	58	10–25 years	O-BD with child diagnosis of: BD (n = 16) ADHD (n = 15) Depressed/anxious (n = 9) Well (n = 18)	Cross-sectional	Thought problem elevations were significantly higher in O-BD with BD than O-BD well children but not significantly different in O-BD with BD versus ADHD or depression/anxiety
Diler et al. 2011 (76)	CBCL	589	6–18 years	O-BD with BD (n = 35) O-BD without BD (n = 319) O-Well (n = 235)	Cross-sectional	Thought problem elevations were significantly higher in O-BD with BD than O-Well children but not different in O-BD with BD versus O-BD without BD or O-BD without BD versus O-Well children. However, O-BD without BD had greater dimensional psychopathology than O-Well children on other CBCL scales
Giles et al.2007 (77)	CBCL	103	10–18 years	O-BD with BD (n = 28) O-BD without BD (n = 31) O-Well(n = 44)	Cross-sectional	Thought problem elevations were significantly higher in O-BD with BD than O-BD without BD and O-Well children. Thought problems were not significantly higher in O-BD without BD than O-Well children
Harvey et al. 1982(94)	TAT Rochester–Martin Code System	157	7–18 years	O-BD (n = 38) O-SZ (n = 23) O-MDD (n = 43) O-Well (n = 53)	Cross-sectional	O-BD generally performed similarly to O-Well on cohesive ties while O-MDD and O-SZ performed worse; O-BD performed better than O-SZ but worse than O-Well on reference patterns O-BD were significantly consistently more deviant than O-Well
Klimes-Dougan et al. 2010 (79)	CBCL	94	6, 9, 13, and 17 years of age at Times 1–4	O-BD (n = 22) O-MDD (n = 42) O-Well (n = 30)	Longitudinal	O-BD and O-MDD had significantly more discontinuity of externalizing problems cascading into thought problems than O-Well with tentative evidence that O-BD had the highest levels of discontinuity, although not statistically higher than O-MDD
Klimes-Dougan et al., in press (17)[a]	CBCL	192	4, 7, 11, 15, and 22 years of age at Times 1–5	O-BD (n = 48) O-MDD (n = 84) O-Well (n = 60)	Longitudinal	The risk for developing any thought problem was significantly higher in O-BD than O-Well and marginally higher in O-BD than O-MDD. In addition, persistence of any thought problems across time was significantly greater in O-BD than O-Well
LaRoohe et al. 1985(59)	CPRS	39	5–18 years	O-BD with a DSM diagnosis (n = 9) O-BD without a DSM diagnosis (n = 30)	Cross-sectional	O-BD with a DSM diagnosis had significantly higher psychotic cluster scores than O-BD without a DSM diagnosis
Numberger et al. 2012 (85)[a]	DIGS WASH-U-KSADS	232	12–21 years	O-BD (n = 141) O-Well (n = 91)	Cross-sectional	5.7% (8/141) of O-BD had psychotic symptoms, compared to 0% of O-Well, but this was not statistically significant

Study	Measure	N	Age	Comparison group(s)	Type of study	Summary of findings
Petresco et al. 2009 (78)	CBCL YSR	149	6–18 years	O-BD (n = 43) O-Other (n = 53) O-Well (n = 53)	Cross-sectional	Level of thought problems on the CBCL was significantly higher in O-BD than O-Other or O-Well; however, there were no significant group differences in level of thought problems on the YSR
Reichart et al. 2004 (74)	CBCL YSR TRF YABCL	132	12–13 years	O-BD compared to other epidemiological samples	Cross-sectional	Level of thought problems on the YSR was significantly higher in O-BD than comparison samples; however, there were no significant group differences in level of thought problems on the other measures
Wals et al. 2001 (75)	CBCL YSR TRF	140	12–21 years	O-BD compared to Dutch and North-American normative samples	Cross-sectional	Thought problem elevations on the CBCL were significantly higher in O-BD males than normative samples Thought problems on the YASR were significantly lower in O-BD males Thought problems on the TRF were significantly lower in O-BD females

ADHD = attention-deficit hyperactivity disorder; CBCL = Child Behavior Checklist; CPRS = Children's Psychiatric Rating Scale; DIGS = Diagnostic Interview for Genetic Studies; K-SADS-PL = The Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (WASH-U = Washington University version); O-BD = offspring of a parent with bipolar disorder (BD); O-MDD = offspring of a parent with major depressive disorder (MDD); O-Other = offspring of a parent with a psychiatric disorder other than BD; O-SZ = offspring of a parent with schizophrenia; O-Well = offspring of psychiatrically well parents; SNAP = Schedule for Nonadaptive and Adaptive Personality; TAT = Thematic Apperception Test; TRF = Teacher Report Form; YABCL = Young Adult Behavior Checklist; YASR = Young Adult Self-Report; YSR = Youth Self-Report.

[a] Also reviewed in Table 1.