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Review article

The search for neuroimaging and cognitive endophenotypes: A critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder

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ABSTRACT

The phenomenology and underlying pathophysiology of bipolar disorder (BD) are heterogeneous. The identification of putative endophenotypes for BD can aid in the investigation of unique patho-etiological pathways, which may lead to the development of personalised preventative and therapeutic approaches for this multi-faceted disorder. We included original studies involving unaffected first-degree relatives of BD patients (URs) and a healthy control (HC) comparison group with no first-degree family history of mental disorders, investigating: 'cold' and 'hot' cognition and functional and structural neuroimaging. Seventy-seven cross-sectional studies met the inclusion criteria. The present review revealed that URs in comparison with HCs showed: (i) widespread deficits in verbal memory, sustained attention, and executive function; (ii) abnormalities in the reactivity to and regulation of emotional information along with aberrant reward processing, and heightened attentional interference by emotional stimuli; and (iii) less consistency in the findings regarding structural and resting state neuroimaging, and electrophysiological measures.

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Abbreviations: ACC, anterior cingulate cortex; CPT, continuous performance task; dlPFC, dorsolateral prefrontal cortex; DSM, the Diagnostic and Statistical Manual of Mental Disorders; DTI, diffusion tensor imaging; EEG, electroencephalogram; ERP, event-related potential; HC, healthy controls; ICD, the International Classification of Diseases; mOFC, medial orbito-frontal cortex; mPFC, medial prefrontal cortex; omPFC, orbito-medial prefrontal cortex; SC, Schizophrenia; SCWT, Stroop Colour Word Task; TMT, Trail making task; UD, unipolar depression; UR, healthy, unaffected first-degree relatives of patients with BD; vACC, ventral anterior cingulate cortex; VBM, voxel based morphology; VLPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefronal cortex; WAIS, Wechsler Adult Intelligence Scale; WM, working memory; WMH, white matter hyper intensities; WMS, Wechsler Memory Scale.

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1. Introduction

Bipolar disorder (BD) is a common chronic illness that is characterised by extreme mood fluctuations and substantial cognitive impairment (Goodwin and Jamison, 2007; Grande et al., 2016). Although compelling evidence indicates that BD is associated with a high degree of heritability (e.g., Goes, 2016; Kieseppä et al., 2004; McGuffin et al., 2003), its exact pathophysiology remains elusive and involves a complex set of gene-environment interactions (Uher, 2014). Replication of genome wide association studies have proven to be difficult due to the complexity of the disorder, differences in diagnostic criteria, methodological challenges, and possible patho-etiological heterogeneity (Gatt et al., 2015; Kerner, 2015; McCarroll et al., 2014), although notably a recent study identified some putative biological pathways involved in the genetic predisposition to BD (e.g., hormonal regulation, calcium cannels; see Nurnberger et al., 2014). Endophenotypes are disease-associated traits that are highly heritable, associated with the illness, independent of the clinical state, and found in non-affected family members to a greater extent than in the general population (Gershon and Goldin, 1986; Gottesman and Gould, 2003; Leboyer et al., 1998). The past decades, the field has witnessed an intensive research effort in to putative endophenotypes for BD, which may improve the understanding of disease heterogeneity through biological validation and phenotype stratification (Hasler et al., 2006; Kerner, 2015).

The search for candidate endophenotypes for BD has revealed substantial evidence for trait-related abnormalities across several neurocognitive domains (Balanza-Martinez et al., 2008) and neuroimaging measures (Hozer and Houenou, 2016; Wu et al., 2016). However, studies in unaffected relatives (URs) of BD patients have produced less uniform evidence for changes in neurocognitive function and neuroimaging measures. It is therefore crucial to evaluate which abnormalities are most consistently exhibited in genetically predisposed individuals to identify the most promising candidate endophenotypes for BD. These efforts may lead to identification of the most consistent biological pathways in BD.

Cognitive deficits are candidate endophenotypes of BD (e.g., Bora et al., 2009b; Glahn et al., 2010). These include disturbances in both 'cold' (i.e., non-emotional) and 'hot' (i.e., emotion-laden) cognition (Roiser and Sahakian, 2013). Trait-related deficits in 'cold' cognition have been repeatedly reported in individuals with BD across several neurocognitive domains, particularly within verbal memory and executive function (Bourne et al., 2013; Robinson et al., 2006; Torres et al., 2007), as well as in their unaffected relatives (Arts et al., 2008; Balanza-Martinez et al., 2008). Although changes in the processing of emotional information and emotional regulation are core abnormalities in mood disorders (Miskowiak and Carvalho, 2014; Phillips et al., 2008), these aspects of 'hot' cognition have only recently become a focus of scientific investigation in URs of patients with mood disorders. These studies suggest that emotion dysregulation is not only present in BD during acute mood episodes (Almeida and Phillips, 2013; Phillips et al., 2008) and in remission (Townsend et al., 2013), but also occur in genetically predisposed individuals (Heissler et al., 2014; Kanske et al., 2015).

Functional and structural imaging studies of BD have revealed fronto-limbic functional abnormalities (Chen et al., 2011a; Strakowski et al., 2012; Strakowski et al., 2005) coupled with structural changes, such as lateral ventricle enlargement (Arnone et al., 2009; Kempton et al., 2008; McDonald et al., 2004). However, little research has been conducted on URs of patients with BD (Mathias de Almeida et al., 2013). Functional neuroimaging studies of resting state activity in the prefrontal cortex, anterior cingulate cortex, and mesolimbic structures that subserve processing of emotionally-laden stimuli and emotion regulation show promise in revealing putative brain-based endophenotypes (Phillips and Vieta, 2007; Vargas et al., 2013). Indeed, aberrant neural response seems to be a more sensitive assay of abnormal brain function than overt behavioural or subjective measures (Haas et al., 2007). Nevertheless, the search for neuroimaging endophenotypes and a precise neuroimaging biosignature for BD has revealed discrepant findings (Phillips and Swartz, 2014) due to small and heterogeneous samples and different methodological approaches (Phillips and Kupfer, 2013).

The aim of the present systematic review is to: (i) synthesise the extant findings in 'hot' and 'cold' cognition and structural and functional neuroimaging measures in unaffected first-degree relatives (URs), i.e., with no history of psychosis or mood disorder, of patients with in comparison with healthy controls (HCs); and in particular, (ii) to clarify which of the abnormalities within these domains constitute the most promising endophenotypes of BD that deserve further investigation in meta-analytical studies.

2. Methods

2.1. Search strategy

Computerised searches on the PubMed/MEDLINE, EMBASE, and PsychInfo databases were performed from inception up until April 2016 (see supplementary online material for the detailed search strategy used in this systematic review). Two reviewers independently performed title/abstract screening (kappa = 0.90). Disagreements were discussed and consensus was reach in all cases. Full-texts of potentially eligible articles were retrieved and both reviewers considered these unique references for inclusion/exclusion during the secondary screening. The search strategy was augmented through tracking the citations of eligible articles in Google Scholar. This systematic review has followed the procedures of the *Preferred reporting items for systematic reviews and* meta-analyses (PRISMA) statement (Moher et al., 2009).

2.2. Selection criteria

We included original peer-reviewed articles involving: (a) first-degree unaffected relatives (URs) of individuals meeting Diagnostic and Statistical Manual of Mental Disorders (DSM) (Association, 2013) or International Classification of Diseases (ICD) (Organization, 1992) criteria for BD (including discordant twins) and a healthy control (HC) comparison group; (b) a diagnosis of BD established through a validated structured diagnostic interview; (c) investigated 'hot' or 'cold' cognition, functional or structural neuroimaging, and/or evoked potentials (ERP); (d) articles published in English, Portuguese, Spanish, Danish, German or French. We excluded articles that: (a) included samples with several diagnoses (unless data for BD was reported separately); (b) studies in which URs and HCs were not directly compared; (c) studies in which first-degree relatives and/or HCs had a history of psychosis, mood disorder, and/or substance use disorders to avoid confounding variables of interest; (d) genetic studies; and (e) meeting abstracts, reviews, and case reports. Whenever studies provided data from overlapping samples, we included only the report that included the largest dataset. In case of doubt, the corresponding author was contacted by e-mail. If reports with sample duplication investigated different variables of interest (i.e., within different overarching themes of interest and/or within different subdomains of cold cognition), both were included.

For studies on 'cold' cognition, we grouped the results of the individual neuropsychological tests into cognitive categories based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), except for verbal fluency which was separated from processing speed, according to the approach adopted by Bora and Pantelis (2015). The neuropsychological tests that were not part of the MATRICS were classified under the relevant cognitive domains based on factor loadings as reviewed by Rodriguez-Jimenez et al. (2012). Further, in accordance to the International Society for BD Task Force on neurocognition, we also included an 'executive function' domain to include response inhibition, cognitive flexibility, and attention switching (Van Rheenen and Rossell, 2014). Effect sizes were estimated whenever a given cognitive finding was clearly replicated across studies.

3. Results

After removal of duplicated hits, 1799 unique references were initially screened. After reviewing their title/abstracts, 493 full-text articles were examined for eligibility. Of these 493 articles, **77** met inclusion criteria and were included in this review; 36 studies investigated 'cold' cognition alone, 21 studies assessed 'hot' cognition alone, 22 assessed neuroimaging alone, nine investigated 'cold' and 'hot' cognition, four investigated 'cold' cognition and neuroimaging, and two studies included all three areas of interest. Fig. 1 depicts the PRISMA flowchart. Given the amount of evidence in some of the aforementioned fields, when more than 10 studies are cited, we refer to the respective table for an overview of the data.

3.1. Cognitive endophenotypes

3.1.1. 'Cold' cognition

As seen from Table 1, 51 studies investigated 'cold' cognition (Adleman et al., 2014; Antila et al., 2007; Besnier et al., 2009; Bora et al., 2008; Brotman et al., 2014; Brotman et al., 2009; Brotman et al., 2008b; Chang and Lenzenweger, 2005; Christodoulou et al., 2012a,b; Civil Arslan et al., 2014; Costafreda et al., 2009; Daban et al., 2012; Deveci et al., 2013; Deveney et al., 2012; Dima et al., 2016; Doyle et al., 2009; Erk et al., 2014; Erol et al., 2014; Frangou, 2012; Frangou et al., 2005; Frantom et al., 2008; Hıdıroğlu et al., 2015; Juselius et al., 2009; Keri et al., 2001; Kim et al., 2015; Kim et al., 2012; Kosger et al., 2015; Kulkarni et al., 2010; Ladouceur et al., 2008; Li et al., 2015; Linke et al., 2013; Maziade et al., 2009; Nehra et al., 2014; Olsavsky et al., 2012; Patino et al., 2013; Pattanayak et al., 2012; Seidel et al., 2012; Sepede et al., 2012; Singh et al., 2014b; Sobczak et al., 2003; Sobczak et al., 2002; Szoke et al., 2006a,b; Teixeira et al., 2014; Thermenos et al., 2011; Trivedi et al., 2008; Tseng et al., 2015; Versace et al., 2010; Wessa et al., 2015; Zalla et al., 2004); these examined general intellectual functioning (k = 31; N = 844 URs, 1040 HCs), speed of processing (k = 14; N = 630 URs, 551 HCs), attention/vigilance (k = 13; N = 408 URs, 396 HCs), verbal learning and memory (k = 18; N = 654 URs, 635 HCs), visual learning and memory (k = 9; N = 341 URs, 389 HCs), reasoning and problem solving (k = 20; N = 718 URs, 734 HCs), working memory (k = 12; N = 390 URs, 412 HCs), verbal fluency (k = 12; N = 307 URs, 440 HCs), and executive function (k = 25; N = 888 URs, 981 HCs) (for an overview and study details see Table 1).

3.1.2. General intellectual functioning

All but one small study (Frantom et al., 2008) found no difference between URs and HCs on IQ measures, which indicates that general intelligence is not an illness-trait conferring genetic liability for BD.

3.1.3. Speed of processing

Nine of 11 studies using the Trail Making Test A (TMT-A) showed no reduction in speed of processing in URs (Table 1). A recent study found that only URs with two or more relatives with BD displayed poorer psychomotor speed, suggesting a possible influence of genetic load on this cognitive domain (Kosger et al., 2015). In contrast, two of four (i.e., half) studies using the WAIS digit symbol subtest revealed slower performance in URs (Antila et al., 2007; Daban et al., 2012), possibly executive function and memory elements in this test. However, overall these finding provide little indication for slower psychomotor speed in URs.

3.1.4. Attention/Vigilance

Of studies investigating sustained attention (k = 13), half found impaired performance in URs (Adleman et al., 2014; Brotman et al.,

Table 1
Eligible studies (k = 51) in which different domains related to 'cold' cognition were compared between unaffected relatives and healthy controls.

Author	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Finding
Intelligence							
Antila et al. (2007)	WAIS-R: Vocabulary subtest	Behaviour	40 URs, 55 HCs	51.4 (9.1)	53	Mixed	URs = HCs
Bora et al. (2008)	WAIS-R: Information subtest	Behaviour	34 URs, 25 HCs	45.7 (12.2)	59	Siblings, parents	URs = HCs
Brotman et al. (2008b)	WASI- two scale IQ	Behaviour	25 URs, 36 HCs	12.15 (3.05)	28	Offspring, siblings	URs = HCs
Brotman et al. (2009)	WASI –FSIQ	Behaviour	26 URs, 24 HCs	12.0 (3.0)	31	Offspring, siblings	URs = HCs
Brotman et al. (2014)	WASI- FSIQ	Behaviour	15 URs, 29 HCs	14.5 (2.2)	40	Offspring, siblings	URs = HCs
Christodoulou et al. (2012a,b)[a]	WAIS-R: Vocabulary Subtest	Behaviour	17 URs, 23 HCs	38.7 (13.4)	76	Mixed	URs = HCs
Costafreda et al. (2009)	WASI verbal IQ	fMRI	7 URs, 48 HCs	39.4 (15.8)	86	Co-twins	URs = HCs
Daban et al. (2012)	WAIS-III: Vocabulary sub-test	Behaviour	50 URs, 60 HCs	39.3 (13.7)	67	–	URs = HCs
Deveney et al. (2012)	WASI two-scale IQ	Behaviour, fMRI	13 URs, 21 HC	13.5 (1.8)	54	Offspring, siblings	URs = HCs
Doyle et al. (2009)	WISC-III or WAIS-III: Vocabulary and block design subtest	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs = HCs
Erk et al. (2014)	Mehrfachwahl-Wortschatz-Intelligenztes (verbal IQ)	Behaviour, fMRI	59 URs, 110 HCs	31.8 (11.8)	61	Mixed	URs = HCs
Frangou et al. (2005)	WAIS-R FSIQ	Behaviour	15 URs, 43 HCs	27.2 (8.9)	67	Offspring	URs = HCs
Frangou (2012)	WAIS-R FSIQ	Behaviour, fMRI	48 URs 71 HCs	36.5 (13.8)	52	Siblings, offspring	URs = HCs
Frantom et al. (2008)	WAIS III: Vocabulary and block design subtests	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs < HCs
Keri et al. (2001)	WAIS-R FSIQ	Behaviour	20 URs, 20 HCs	35.1 (9.5)	60	Siblings	URs = HCs
Kim et al. (2015)	Korean WAIS: Vocabulary and block design	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	URs = HCs
Ladouceur et al. (2008)	WISC-III: FSIQ	Behaviour	20 URs, 22 HCs	13.0 (2.7)	55	Offspring	URs = HCs
Linke et al. (2013)	Multiple Choice Word Vocabulary (IQ)	Behaviour	22 URs, 22 HCs	28.0 (11.0)	50	Siblings, offspring	URs = HCs
Maziade et al. (2009)	WISC-III or WAIS-III for relatives and WASI for relatives	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs < HCs
Olsavsky et al. (2012)	WASI FSIQ	Behaviour	13 URs, 56 HCs	14.0 (2.4)	46	Offspring, siblings	URs = HCs
Seidel et al. (2012)	Mehrfachwahl-Wortschatz-Intelligenztes (verbal IQ)	Behaviour	21 URs, 21 HCs	38.4 (17.7)	48	–	URs = HCs
Sepede et al. (2012)	WAIS FSIQ	Behaviour, fMRI	22 URs, 24 HCs	31.5 (7.3)	68	Offspring, siblings	URs = HCs
Singh et al. (2014b)	WASI FSIQ	Behaviour	20 URs, 25 HCs	12.7 (2.9)	65	Offspring	URs = HCs
Sobczak et al. (2002)	Groninger Intelligence Test (GIT)	Behaviour	30 URs, 15 HCs	41.4 (2.6)	73	Mixed	URs = HCs
Sobczak et al. (2003)	Groninger Intelligence Test (GIT)	Behaviour	30 URs, 15 HCs	41.0 (2.9)	67	Mixed	URs = HCs
Teixeira et al. (2014)	WASI (no info if full scale or not)	Behaviour	18 URs, 20 HCs	12.7 (3.1)	50	Offspring	URs = HCs
Thermenos et al. (2011)	WAIS or WISC (Estimated IQ with eight subtest)	Behaviour, fMRI	10 URs, 10 HCs	18.4 (4.2)	50	–	URs = HCs
Versace et al. (2010)	WASI FSIQ	Behaviour	20 URs, 25 HCs	13.2 (2.5)	45	Offspring	URs = HCs

Wessa et al. (2015)	German Culture Fair Intelligence test	Behaviour	27 URs, 29 HCs	31.8 (14.4)	52	–	URs = HCs
Zalla et al. (2004)	WAIS-R FSIQ	Behaviour	33 URs, 20 HCs	37.3 (11.0)	61	Parents, siblings	URs = HCs
Speed of processing							
Antila et al. (2007)	TMT A, Digit Symbol	Behaviour	40 URs, 55 HCs	51.4 (9.1)	53	Mixed	Digit Symbol: UR< HC; TMT A: UR = HC
Arslan et al. (2014)	TMT A	Behaviour	55 URs, 32 HCs	37.7 (3.6)	56	Mixed	URs = HCs
Bora et al. (2008)	TMT A	Behaviour	34 URs, 25 HCs	45.7 (12.2)	59	Siblings, parents	URs = HCs
Daban et al. (2012)	Digit symbol	Behaviour	50 URs, 60 HCs	39.3 (13.7)	67	–	URs< HCs
Deveci et al. (2013)	TMT A	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	URs < HCs
Doyle et al. (2009)	Digit Symbol Coding, Digit Symbol Search	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	Digit Symbol Coding: URs = HCs Digit Symbol Search: URs = HCs
Erol et al. (2014)	TMT A	Behaviour	50 URs, 50 HCs	56.2 (6.7)	50	Parents	URs = HCs
Frantom et al. (2008)	TMT A	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs = HCs
Kosger et al. (2015)	TMT A	Behaviour	24 FP (≥ two relatives with BD), 26 SP (One first-degree relative), 26 HCs	FP: 57.5 (7.6); SP: 56.1 (5.8)	FP: 46; SP: 54	Mixed	FPs < HCs; SPs = HCs
Kulkarni et al. (2010)	TMT A	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	URs = HCs
Nehra et al. (2014)	Digit substitution	Behaviour	20 URs, 20 HCs	36.9 (8.6)	15	Siblings	URs = HCs
Pattanayak et al. (2012)	TMT A	Behaviour	20 URs, 20 HCs	30.7 (11.4)	40	Mixed	URs = HCs
Szoke et al. (2006b)	TMT A	Behaviour	51 URs, 50 HCs	40.4 (13.3)	63	–	URs = HCs
Szoke et al. (2006a)	TMT A	Behaviour	63 URs, 48 HCs	40.7 (13.0)	61	–	URs = HCs
Attention/vigilance							
Adleman et al. (2014)	The Flanker task	Behaviour	15 URs, 34 HCs	4.6 (0.6)	27	Offspring, siblings	URs < HCs (variability of RT on incongruent trails)
Bora et al. (2008)	Conners' CPT-II	Behaviour	34 URs, 25 HCs	45.7 (12.2)	59	Siblings, parents	URs = HCs
Brotman et al. (2009)	Flanker CPT	Behaviour	26 URs, 24 HCs	12.0 (3.0)	31	Offspring, siblings	URs < HC
Deveci et al. (2013)	Test of variables of attention (TOVA)	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	URs = HCs
Doyle et al. (2009)	Seidman auditory CPT	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs < HCs
Frantom et al. (2008)	CPT	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs = HCs
Kim et al. (2015)	Auditory and visual CPT	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	URs = HCs
Kulkarni et al. (2010)	CPT	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	URs = HCs
Maziade et al. (2009)	CPT-II	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs = HCs
Patino et al. (2013)	The Eriksen Flanker Task	Behaviour	22 URs, 20 HCs	15.0 (3.0)	46	Offspring	URs < HCs
Sepede et al. (2012)	Degraded stimulus CPT	Behaviour, fMRI	22 URs, 24 HCs	31.5 (7.3)	68	Offspring, siblings	Behaviour: URs < HCs. ↑activation in bilateral insula and posterior middle cingulate cortex during non-correct target response. During correct target response, URs showed ↑ deactivation of posterior cingulate, and only during stimuli degradation ↑activity in left insula and bilateral inferior parietal lobule.

Table 1 (*Continued*)

Author	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Finding
Sobczak et al. (2003)	Dichotic Listening task (DLT), Left/right Choice reaction time (CRT), Motor choice reaction time (MRCT)	Behaviour	30 URs, 15 HCs	41.0 (2.9)	67	Mixed	DLT: URs<HCs, MCR; Us<HCs, CRT URs = HCS. (FH I vs. II: DLT: URs = HCs, MRCT: URs<HCs, CRT URs = HCs. Group x TRP loading interaction: DLT: URs = HC, MCRT: URs = HCS, CRT: URs>HCs)
Trivedi et al. (2008)	CPT	Behaviour	10 URs, 10 HCs	30.1 (11.2)	10	Siblings	URs < HCs
Verbal learning and memory							
Antila et al. (2007)	CVLT	Behaviour	40 URs, 55 HCs	51.4 (9.1)	53	Mixed	URs = HCs
Arslan et al. (2014)	RAVLT	Behaviour	55 URs, 32 HCs	37.7 (3.6)	56	Mixed	URs < HCs
Bora et al. (2008)	RAVLT	Behaviour	34 URs, 25 HCs	45.7 (12.2)	59	Siblings, parents	URs = HCs
Chang and Lenzenweger (2005)	The Miller-Selfridge Task	Behaviour	30 URs, 30 HCs	–	47	–	URs = HCs
Christodoulou et al. (2012a)	CVLT	Behaviour	17 URs, 23 HCs	38.7 (13.4)	76	Mixed	URs < HCs
Deveci et al. (2013)	RAVLT	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	URs < HCs
Doyle et al. (2009)	CVLT-II (trails 1–5 only)	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs = HCs
Erk et al. (2014)	Verbal learning and memory task (VLMT)	Behaviour	59 URs, 110 HCs	31.8 (11.8)	61	Mixed	URs = HCs
Frantom et al. (2008)	CVLT	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs = HCs
Keri et al. (2001)	Verbal recall and recognition	Behaviour	20 URs, 20 HCs	35.1 (9.5)	60	Siblings	URs < HCs
Kim et al. (2015)	K-AVLT	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	URs = HCs
Kosger et al. (2015)	CVLT	Behaviour	24 FP (≥ two relatives with BD), 26 SP (One first-degree relative), 26 HCs	FP: 57.5 (7.6); SP: 56.1 (5.8)	FP: 46; SP: 54	Mixed	FD < HCs, SP = HCs
Kulkarni et al. (2010)	RAVLT	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	URs < HCs
Maziade et al. (2009)	CVLT	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs < HCs
Nehra et al. (2014)	Hopkins verbal learning test-revised (HVLT-R)	Behaviour	20 URs, 20 HCs	36.9 (8.6)	15	Siblings	URs < HCs
Pattanayak et al. (2012)	PGI Memory Scale	Behaviour	20 URs, 20 HCs	30.7 (11.4)	40	Mixed	URs = HCs
Sobczak et al. (2002)	Visual verbal learning task (VVLT)	Behaviour	30 URs, 15 HCs	41.4 (2.6)	73	Mixed	URs < HCs. URs(BD I) < URs(BDII). Group x trp depletion effects: URs = HCs
Sobczak et al. (2003)	Visual verbal learning task (VVLT)	Behaviour	30 URs, 15 HCs	41.0 (2.9)	67	Mixed	URs < HCs. URs(BDI) < URs(BDII). Group x trp loading interaction: URs = URs
Visual learning and memory							
Doyle et al. (2009)	Rey-Osterreich Complex figure	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs = HCs
Erk et al. (2014)		fMRI	59 URs 110 HCs	31.8 (11.8)	61	Mixed	↓ activity in left and right hippocampus and pgACC

Frantom et al. (2008)	Rey-Osterrieth Complex Figure (ROCF), Biber Figure Learning Test-Extended (Biber), Faces I and II subtests of the Wechsler Memory Scale III, Benton Facial Recognition	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	Biber 1–5 trail: URs < HCs, ROCF:URs < HCs, ↓ performance on WMS Faces I. No other group differences.
Kim et al. (2015)	K- Complex figure task	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	URs = HCs
Kulkarni et al. (2010)	Rey's Complex Figure Test	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	URs < HCs
Maziade et al. (2009)	Rey complex figure	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs < HCs
Nehra et al. (2014)	Brief visuospatial memory test-revised	Behaviour	20 URs, 20 HCs	36.9 (8.6)	15	Siblings	URs = HCs
Sobczak et al. (2002)	Picture learning task	Behaviour	30 URs, 15 HCs	41.4 (2.6)	73	Mixed	URs = HCs. FH I vs. FH II:URs = HCs. Group x Trp depletion effects: URs = HCs.
Tseng et al. (2015)	Emotional face encoding	Behavioural, fMRI	13 URs, 37 HCs	13.7 (2.3)	39	Offspring, sibling	↓ activation in middle frontal gyrus and ↑ activation in parahippocampal gyrus during successful vs. unsuccessful encoding.
Reasoning and problem solving							
Arslan et al. (2014)	WCST	Behaviour	55 URs, 32 HCs	37.7 (3.6)	56	Mixed	URs < HCs
Bora et al. (2008)		Behaviour	34 URs, 25 HCs	45.7 (12.2)	59	Siblings, parents	URs < HCs
Deveci et al. (2013)	WCST	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	URs = HCs
Doyle et al. (2009)	WCST	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs < HCs
Erol et al. (2014)	WCST	Behaviour	50 URs, 50 HCs	56.2 (6.7)	50	Parent	URs = HCs
Frangou et al. (2005)	WCST	Behaviour	15 URs, 43 HCs	27.2 (8.9)	67	Offspring	URs > HCs
Frantom et al. (2008)	WCST, Wechsler Block Design	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	Wechsler Block Design: URs < HCs, WCST: URs = HCs
Juselius et al. (2009)	WCST	Behaviour	19 URs, 114 HCs	45.8 (1.7)	32	Co-twins	URs = HCs
Kim et al. (2015)	WCST	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	URs = HCs
Kosger et al. (2015)	WCST	Behaviour	24 FD (≥ two relatives with BD), 26 SP (One first-degree relative), 26 HCs	FP: 57.5 (7.6); SP: 56.1 (5.8)	FP: 46; SP: 54	Mixed	FD < HCs. SP < HCs
Kulkarni et al. (2010)	WCST, TOL	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	TOL: URs < HCs; WCST: URs = HCs
Li et al. (2015)	WCST	Behaviour	20 URs, 20 HCs	40.6 (10.5)	45	Siblings	URs = HCs
Linke et al. (2013)	The Intra-Extra Dimensional Set Shift Task	Behaviour	22 URs, 22 HCs	28.0 (11.0)	50	Siblings, offspring	URs < HCs
Maziade et al. (2009)	WCST, TOL	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	WCST: URs < HCs
Nehra et al. (2014)	WCST	Behaviour	20 URs, 20 HCs	36.9 (8.6)	15	Siblings	URs = HCs
Sobczak et al. (2002)	Compu-TOL	Behaviour	30 URs, 15 HCs	41.4 (2.6)	73	Mixed	URs < HCs, FH I vs. FH II: FH I < FH II. Group by Trp depletion: URs < HCs.
Sobczak et al. (2003)	Compu-TOL	Behaviour	30 URs, 15 HCs	41.0 (2.9)	67	Mixed	URs = HCs; FH I vs. FH II: FH I = FH II. Group by Trp loading: URs = HCs
Szoke et al. (2006b)	WCST	Behaviour	51 URs, 50 HCs	40.4 (13.3)	63	–	URs = HCs

Table 1 (*Continued*)

Author	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Finding
Szoke et al. (2006a)	WCST	Behaviour	63 URs, 48 HCs	40.7 (13.0)	61	–	URs = HCs
Trivedi et al. (2008)	WCST	Behaviour	10 URs, 10 HCs	30.1 (11.2)	10	Siblings	URs < HCs
Working memory							
Antila et al. (2007)	Digit Span Forward and Backward (WMS-R), Visual Span Forward and Backward (WMS-R)	Behaviour	40 URs, 55 HCs	51.4 (9.1)	53	Mixed	Visual Span Backward task: URs < HCs
Bora et al. (2008)	Auditory Consonant Trigrams (ACTT), Digit Span forward and Backward, Letter-Number Sequencing,	Behaviour	34 URs,25 HCs	45.7 (12.2)	59	Siblings, parents	ACTT total, Digits backward, Letter-Number Sequencing: URs < HCs. Digits forward: URs = HCs
Deveci et al. (2013)	Digit span Forward and backward (DST) Auditory consonant trigram test (ACTT)	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	ACTT, digit span forward: URs < HCs. Digit span backward: URs = HCs
Doyle et al. (2009)	WAIS-III: Arithmetic subset	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs = HCs
Dima et al. (2016)	N-back WM paradigm	Behaviour, fMRI	25 URs, 46 HCs	39.7 (13.7)	48	Siblings	Behavioural: URs > HCs (accuracy 3-back condition); fMRI: ↑ activation of bilateral middle, inferior frontal gyrus, right temporal gyrus and bilateral ACC; no difference in endogenous connections.
Frantom et al. (2008)	Digit Span, Spatial Span	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs = HCs
Keri et al. (2001)	Span tasks	Behaviour	20 URs, 20 HCs	35.1 (9.5)	60	Siblings	URs = HCs
Kim et al. (2015)	Digit Span forward and backward	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	Backward digit span: URS < HCs. Forward Digit Span: URs = HCs
Linke et al. (2013)	WAIS: digit span subtest	Behaviour	22 URs, 22 HCs	28.0 (11.0)	50	Siblings, offspring	URs = HCs
Maziade et al. (2009)	WAIS Digit span subtest, Corsi (working memory)	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs = HCs
Pattanayak et al. (2012)	Verbal Working Memory N-Back Test	Behaviour	20 URs, 20 HCs	30.7 (11.4)	40	Mixed	URs = HCs
Thermenos et al. (2011)	2-back and 0-back control WM task	Behaviour, fMRI	10 URs, 10 HCs	18.4 (4.2)	50	–	Behaviour: URs = HCs. fMRI: ↓activation in Cerebellar vermis on 2 back ↑during 0-back condition. ↓ activity in frontopolar region and ↑activity in brain stem, CV, insula, and amygdala (0-back > fixation contrast). No differences in OFC.

Verbal fluency							
Christodoulou et al. (2012b)	Controlled oral work association test	Behaviour	17 URs, 23 HCs	38.7 (13.4)	76	Mixed	URs < HCs
Costafreda et al. (2009)	Letter fluency Task	fMRI	7 URs, 48 HCs	39.4 (15.8)	86	Co-twins	URs = HCs
Deveci et al. (2013)	Controlled word association test	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	URs < HCs
Erol et al. (2014)	Verbal fluency test	Behaviour	50 URs, 50 HCs	56.2 (6.7)	50	Parents	URs = HCs
Frantom et al. (2008)	Controlled oral work association	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs = HCs
Juselius et al. (2009)	Letter fluency Test, Semantic fluency Test	Behaviour	19 URs, 114 HCs	45.8 (1.7)	32	Co-twins	URs = HCs
Keri et al. (2001)	Letter fluency	Behaviour	20 URs, 20 HCs	35.1 (9.5)	60	Siblings	URs = HCs
Kim et al. (2015)	Verbal fluency Test	Behaviour	29 URs, 34 HCs	31.8 (8.0)	59	–	URs = HCs
Maziade et al. (2009)	Verbal fluency task	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs < HCs
Sobczak et al. (2002)	Verbal fluency test	Behaviour	30 URs, 15 HCs	41.4 (2.6)	73	Mixed	URs = HCs; FH I vs FH II: FH I = FH II: Group x TRP depletion: URs = HCs
Sobczak et al. (2003)	Verbal fluency test	Behaviour	30 URs 15 HCs	41.0 (2.9)	67	Mixed	URs = HCs; FH I vs. FH II: FH I = FH II: Group by TRP loading: URs = HCs
Zalla et al. (2004)	Verbal fluency	Behaviour	33 URs, 20 HCs	37.3 (11.0)	61	Parents, siblings	URs = HCs
Executive function							
Antila et al. (2007)	TMT B	Behaviour	40 URs, 55 HCs	51.4 (9.1)	53	Mixed	URs < HCs (%correct)
Arslan et al. (2014)	SCWT, TMT-B	Behaviour	55 URs, 32 HCs	37.7 (3.6)	56	Mixed	URs = HCs
Besnier et al. (2009)	SCWT	Behaviour	30 URs, 60 HCs	41.8 (13.8)	57	Parents, siblings	URs = HCs
Bora et al. (2008)	SCWT, TMT B	Behaviour	34 URs, 25 HCs	45.7 (12.2)	59	Siblings, parents	URs < HCs
Christodoulou et al. (2012b)	Hayling sentence completion task	Behaviour	17 URs, 23 HCs	38.7 (13.4)	76	Mixed	URs = HCs
Deveci et al. (2013)	SCWT	Behaviour	30 URs, 37 HCs	12.3 (2.8)	50	Offspring	URs = HCs
Deveney et al. (2012)	Stop signal task (SST)	Behaviour, fMRI	13 URs, 21 HCs	13.5 (1.8)	54	Offspring, siblings	Stop incorrect vs. Stop correct: ↑ activity in left putamen. Stop incorrect vs. Go: ↑ activity in bilateral putamen. Stop correct vs. go contrast: no group diff. No difference in nucleus accumbens and in whole brain analysis.
Doyle et al. (2009)	SCWT	Behaviour	118 URs, 79 HCs	12.8 (4.0)	47	Siblings	URs < HCs
Erol et al. (2014)	SCWT, TMT B	Behaviour	50 URs, 50 HCs	56.2 (6.7)	50	Parents	URs < HCs
Frangou et al. (2005)	Hayling sentence completion task	Behaviour	15 URs, 43 HCs	27.2 (8.9)	67	Offspring	URs < HCs
Frangou (2012)	SCWT	Behaviour, fMRI	48 URs, 71 HCs	36.5 (13.8)	52	Siblings, offspring	Behaviour: URs = HCs. fMRI: ↓ engagement of the superior and inferior parietal GM, no difference in caudate and VLPFC

Table 1 (*Continued*)

Author	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Finding
Frantom et al. (2008)	SCWT, TMT B	Behaviour	19 URs, 19 HCs	38.3 (15.7)	79	Mixed	URs = HCs
Hidiroglu et al. (2013)	Stop-Signal Task, SCWT	Behaviour	30 URs, 33 HCs	21.0 (8.9)	53	Mixed	URs < HCs
Juselius et al. (2009)	SCWT, TMT B-A	Behaviour	19 URs, 114 HCs	45.8 (1.7)	32	Co-twins	SCWT: URs < HCs, TMT B-A: Urs>HCs
Kim et al. (2012)	The change task	Behaviour, fMRI	13 URs, 21 HCs	13.9 (2.0)	54	Siblings, offspring	Behaviour: no differences. fMRI: Successful change vs. Go:↑ activation in right VLPFC, right inferior parietal lobe, and left cerebellar regions; Unsuccessful change vs. Go:↑ activation in right caudate and left cerebellum; Successful change vs. Unsuccessful change:↑ activation in right VLPFC.
Kosger et al. (2015)	SCWT, TMT B	Behaviour	24 FD (≥ two relatives with BD), 26 SP (One first-degree relative), 26 HCs	FP: 57.5 (7.6); SP: 56.1 (5.8)	FP: 46; SP: 54	Mixed	SCWT: FDs < HCs; SPs < HCs, TMT B: URs < HCs
Kulkarni et al. (2010)	SCWT, TMT B	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	URs = HCs
Maziade et al. (2009)	SCWT	Behaviour	23 URs, 45 HCs	17.5 (4.5)	39	Offspring	URs = HCs
Pattanayak et al. (2012)	SCWT, TMT B	Behaviour	20 URs, 20 HCs	30.7 (11.4)	40	Mixed	SCWT: URs = HCs, TMT B: URs < HCs
Sobczak et al. (2002)	SCWT	Behaviour	30 URs, 15 HCs	41.4 (2.6)	73	Mixed	URs = HCs; FH I vs. FH II: FH I = FH II; Group x Trp depletion:.URs = HCs
Sobczak et al. (2003)	Go/No Go task (GONT)	Behaviour	30 URs, 15 HCs	41.0 (2.9)	67	Mixed	URs = HCS; FH I and FH II: FH I = FHII;Group x Trp loading: URs < HCs
Szoke et al. (2006b)	TMT B	Behaviour	51 URs, 50 HCs	40.4 (13.3)	63	–	Urs = HCs
Szoke et al. (2006a) [b]	TMT B	Behaviour	63 URs, 48 HCs	40.7 (13.0)	61	–	URs < HCs
Wessa et al. (2015)	Stop signal task (SST)	Behaviour	27 URs, 29 HCs	31.8 (14.4)	52	–	URs = HCs
Zalla et al. (2004) [b]	SCWT	Behaviour	33 URs, 20 HCs	37.3 (11.0)	61	Parents, siblings	URs < HCs

Notes: WAIS-R = Wechsler Adult Intelligence Scale (Revised); WASI = Wechsler Abbreviated Scale of Intelligence; WISC = The Wechsler Intelligence Scale for Children; TMT-A = Trial Making Test A; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; RAVLT = Rey auditory-verbal learning test; K-AVLT = Korean version of the Rey auditory verbal learning test; Compu-TOL = Computerised Tower of London test; Trp = Tryptophan; WM = working memory; BDI = type I bipolar disorder; BDII = Type II bipolar disorder; WCST = Wisconsin Card Sorting Test; TMT B – Trial Making Test B; TMT B = Trial Making Test B; SCWT = Stroop Colour Word test; FH1 = URs of type I BD patients; FH2 = URs of type II BD patients; URs = unaffected relatives of subjects with BD; HCs = Healthy Controls.

[a] Overlapping sample.

[b] Partially overlapping sample.

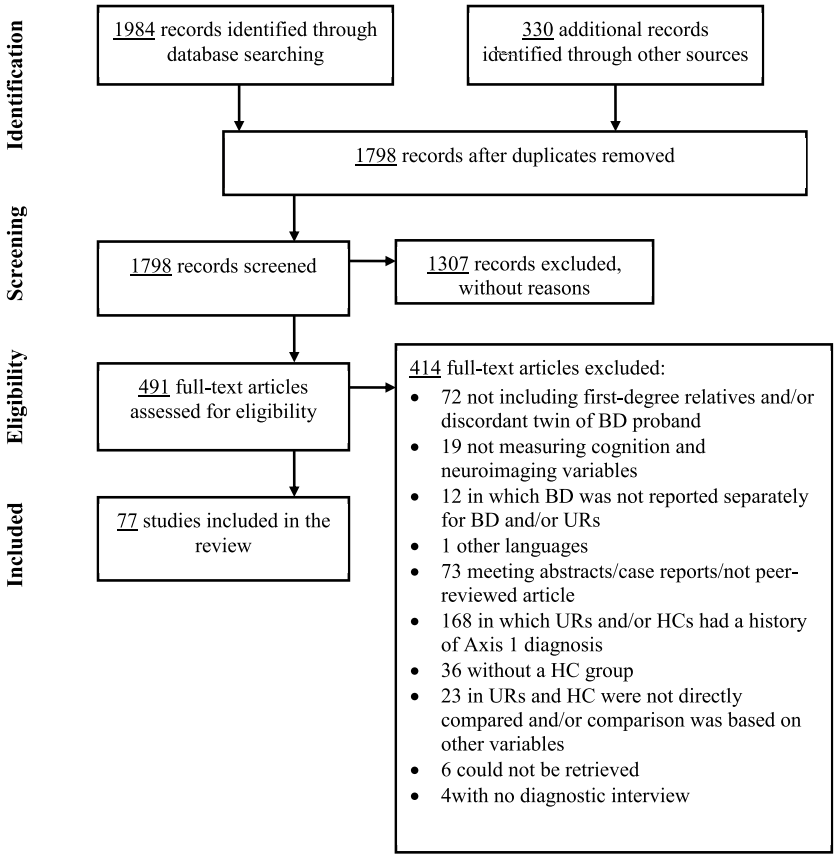


Fig. 1. PRISMA flowchart for study selection for systematic review.
Abbreviations: BD = bipolar disorder; HC = healthy controls; UR = unaffected first-degree relatives of patients with biopalar disorder.

2009; Doyle et al., 2009; Patino et al., 2013; Sepede et al., 2012; Sobczak et al., 2003; Trivedi et al., 2008). This discrepancy is likely due to differences between the implemented tests with ceiling effects in some (less demanding) tests (variations of the CPT: e.g., Conners' vs. TOVA, as well as auditory vs. visual measures; see Table 1). Notably, impairment in sustained attention was more often reported in unaffected children than adults at genetic risk (Adleman et al., 2014; Brotman et al., 2009; Deveci et al., 2013; Doyle et al., 2009; Patino et al., 2013). This could potentially indicate acquisition of compensatory strategies with increasing age as a result of CNS maturation. Neuroimaging examination of URs revealed that sustained attention deficits were accompanied by abnormally increased insula and middle cingulate cortex activity (Sepede et al., 2012). The study also showed increased insula and parietal activation in conditions with greater attentional load in URs, suggesting a need for allocation of greater neural resources to sustain attention (i.e., inefficient processing). Taken together, the findings point to deficits in URs on more challenging sustained attention tests, while other tests with lower attentional demands show only neuronal activity differences.

3.1.5. Verbal learning and memory

Eleven of the 18 studies (61%) of verbal memory in URs detected impairments in immediate and delayed recall and in recognition (see Table 1). The discrepancy across studies may be due to differences in BD subtype (I versus II) in URs' affected family member, as poorer verbal memory outcomes have been reported in URs of BD-I relative to BD-II patients (Kosger et al., 2015; Sobczak et al., 2003; Sobczak et al., 2002). Deficits in verbal learning and memory may thus be associated selectively with genetic liability to BD-I, rather than being a general endophenotype of BD.

3.1.6. Visual learning and memory

Three studies of visuospatial memory identified impaired performance in URs (Frantom et al., 2008; Kulkarni et al., 2010; Maziade et al., 2009), while an equivalent number of studies (k = 4) with larger sample sizes showed no deficits (Doyle et al., 2009; Kim et al., 2015; Nehra et al., 2014; Sobczak et al., 2002). Regarding visual memory for faces, URs displayed impairments on one (Wechsler Memory Scale-III [WMS-III] Faces I) but not on two other tests (WMS-III Faces II or the Benton Facial Recognition Test) (Frantom et al., 2008). Neuroimaging studies in URs showed *hyper*-activation in parahippocampal gyrus and *hypo*-activation in medial PFC regions during encoding of emotional faces (Tseng et al., 2015) as well as *hypo*-activity in the hippocampus and anterior cingulate cortex (ACC) during memory retrieval of faces (Erk et al., 2014). In summary, there is no convincing evidence for visual learning and memory impairments in URs, although emerging evidence points to aberrant neural activity during encoding and retrieval of faces.

3.1.7. Reasoning and problem-solving

Half of studies (k = 10) probing reasoning and problem-solving found worse performance in URs with small to medium effects sizes (see Table 1). One third found impaired performance on the Wisconsin Card Sorting Task (WCST) (Arslan et al., 2014; Bora et al., 2008; Doyle et al., 2009; Kosger et al., 2015; Maziade et al., 2009; Trivedi et al., 2008), while the vast majority of studies using the Tower of London task revealed deficits in URs. Problems with strategic planning may thus be a stronger endophenotype than difficulties with cognitive flexibility (Kulkarni et al., 2010; Maziade et al., 2009; Sobczak et al., 2002). Nevertheless, given the lack of evidence deficits in half of the extant studies suggests that rea-

Table 2
Eligible studies (k = 21) in which domains related to "hot" cognition were investigated in unaffected relatives and healthy controls.

Authors	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Finding
Besnier et al. (2009)	The Emotional Stroop Paradigm	Behaviour	30 URs, 60 HCs	41.8 (13.8)	57	Parents, siblings	↑ emotional interference to disease-associated words
Brand et al. (2012)	Affective Go/No-Go	Behaviour	20 URs, 20 HCs	39.2 (10.5)	70	Siblings	↑ biased responses to negative stimuli
Brotman et al. (2008a)	The Facial Expression subtest of the Diagnostic Analysis of Nonverbal Accuracy Scale	Behaviour	24 URs, 78 HCs	11.5 (4.0)	29	Offspring, siblings	↑ Misidentification of emotions on both child and adult faces.
Brotman et al. (2008b)	Emotional Expression Multimorph Task	Behaviour	25 URs, 36 HC	12.15 (3.05)	28	Offspring, siblings	URs demanded higher facial expression intensity to all facial expressions compared to HCs.
Brotman et al. (2014)	Parametric faces paradigm	Behaviour, fMRI	15 URs, 29 HCs	14.5 (2.2)	40	Offspring, siblings	Behavioural: angry and happy faces rated less hostile by URs than HCs. fMRI: ↓ amygdala modulation with increasingly angry faces. No difference in happy faces. ↓ Modulation of interior frontal gyrus during explicit hostility ratings, ↑ modulation during implicit hostility ratings.
Dima et al. (2016)	Facial affect-recognition paradigm	Behaviour, fMRI	25 URs, 46 HCs	39.7 (13.7)	48	Siblings	Behavioural: URs = HCs; fMRI: ↑ connectivity between the amgydala and the VLPFC, and between IOG and FG.
Giakoumaki et al. (2010)	Startle response to IAPS images	EMG	19 URs, 42 HCs	31.8 (7.4)	–	Siblings	URs scored pleasant and neutral pictures ↑ pos, and unpleasant pictures ↑ neg than HCs. Relatives has ↓ baseline startle amplitude and blunted attentional and affective startle modulation compared to HCs.
Green et al. (2011)	CERQ	Self-report	124 URs, 63 HCs	52.3 (15.7)	62	Parents, siblings	↑ Habitual rumination and self-blame.
Hidiroglu et al. (2013)	The Balloon Analogue Risk Task	Behavioural	25 URs, 30 HCs	40.2 (13.4)	68	Mixed	↑ risk taking propensity (lower adjustment scores).
Kanske et al. (2015)	CERQ, Emotion regulation to IAPS pictures	Self-report, Behaviour, fMRI	17 URs, 17 HCs	36.7 (16.3)	47	Mixed	Self-report: ↓ habitual reappraisal. Behavioural: UR rated positive images less positive, and were less successful at down-regulating positive emotion during reappraisal. fMRI: ↓ down-regulation of amygdala during reappraisal. Reversed amygdala-OFC connectivity.
Kulkarni et al. (2010)	Iowa Gambling Task	Behaviour	30 URs, 30 HCs	28.9 (7.1)	20	Siblings	No difference on IGT.
Ladouceur et al. (2013)	The emotional face N-Back task	Behaviour, fMRI	16 URs, 15 HCs	14.2 (2.3)	44	Offspring	Behavioural: no group differences on accuracy or RT. fMRI: ↑ VLPFC activation to happy face distracters, and ↓ VLPFC modulation of right amygdala to fearful and happy face distracters.

Linke et al. (2012, 2013)[a]	Reversal Learning Task (RLT), Cambridge Gambling Task (CGT)	RLT: Behaviour, fMRI; CGT: Behaviour, DTI	22 URs, 22 HCs	28.0 (11.0)	50	Siblings, offspring	RLT: Behavioural: No diff in RT. fMRI: ↑ activation of mOFC to reward, punishment, and rule reversal, ↑ activation in amygdala to reward and rule reversal. CGT: ↑ risk taking (i.e., points gambled) in URs. Risk taking correlated negatively with FA in the anterior limb of internal capsule for URs and HCs.
Olsavsky et al. (2012)	Facial emotion processing paradigm	Behaviour, fMRI	13 URs, 56 HCs	14.0 (2.4)	46	Offspring, siblings	Behavioural: no group diff in afraid ratings of fearful and happy faces. fMRI: ↑ activation in right amygdala to fearful faces.
Pavlickova et al. (2014)	The Domain-Specific Risk-Taking Test (DOSPERT)	Self-report	30 URs, 30 HCs	15.9 (1.9)	57	Offspring	No differences in risk-taking.
Seidel et al. (2012)	Facial emotion recognition paradigm	Behaviour	21 URs, 21 HCs	38.4 (17.7)	48	–	↓ accuracy in emotion recognition (lowest accuracy for sad faces). ↓ RT to emotional faces. (lowest to fearful faces).
Sepede et al. (2015)	Emotion processing to negative IAPS pictures	fMRI	22 URs, 24 HCs	31.5 (7.3)	68	Offspring, siblings	↑ activation in left insula and right lingual gyrus, ↓ activation in right supramarginal gyrus, pre-supplementary motor area, and right superior frontal gyrus to negative images.
Singh et al. (2014b)	Monetary Incentive Delay Task	Voxel-wise neuroimaging	20 URs, 25 HCs	12.7 (2.9)	65	Offspring	↑ activation in left lateral OFC to reward, ↓ activation in pregenual cingulate to losses, and weaker functional connectivity between the pregenual cingulate and the right VLPFC while anticipating rewards.
Surguladze et al. (2010)	Facial emotion processing paradigm	fMRI	20 URs, 20 HCs	43.0 (13.8)	40	–	↑ activation in mPFC to fearful and happy faces. ↑ activity in left amygdala to intensely happy faces.
Wessa et al. (2015)	Cambridge Gambling Task	Behaviour	27 URs, 29 HCs	31.8 (14.4)	52	–	↑ delay aversion

Notes: URs = unaffected first-degree relatives of individuals with BD; HCs = Healthy controls; IAPS = International Affective Picture System; VLPFC = Ventrolateral prefrontal cortex; EMG = Electromyography; CERQ = Cognitive Emotion Regulation Questionnaire; IOG = Inferior occipital gyrus; FG = Fusiform gyrus; IGT = Iowa Gambling Task; RT = Reversal Learning task; OFG = Orbitofrontal Cortex; mOFG = medial orbitofrontal cortex; mPFC = medial prefrontal cortex.

[a] Overlapping sample.

soning and problem solving difficulty is not a strong candidate endophenotype for BD.

3.1.8. Working memory

Of the 12 studies of working memory (WM), only four found impairments in URs (Antila et al., 2007; Bora et al., 2008; Deveci et al., 2013; Kim et al., 2015). Of these studies, the majority found impairments on the digit/visual span backward test, suggesting that WM tests with greater cognitive demands are needed to uncover WM deficits in URs (i.e., avoiding ceiling effects). Notably, most of these studies specifically investigated URs of BD-I patients, and the findings could thus reflect a specific association between the genetic liability to the BD I subtype. One neuroimaging study revealed *reduced* activity in the (task-relevant) frontopolar cortex coupled with *increased* activity in (task-irrelevant) limbic regions and insula during N-back WM performance (Thermenos et al., 2011). However, another study using a similar N-back task found no differences between URs and HCs on WM network activity or connectivity (Dima et al., 2016). Overall, these findings point to no conclusive association between WM impairment and genetic liability to BD.

3.1.9. Verbal fluency

Three of 12 studies found impairments on verbal fluency in URs with large effect sizes (ranging from 0.6-1.0). The observed impairments were specific to phonemic fluency (i.e., the generation of words starting with a specific letter) as opposed to semantic category (Christodoulou et al., 2012a; Deveci et al., 2013; Maziade et al., 2009). Nevertheless, most studies (k = 9) found no verbal fluency decrease in URs (Erol et al., 2014; Frantom et al., 2008; Juselius et al., 2009; Keri et al., 2001; Kim et al., 2015; Sobczak et al., 2003; Sobczak et al., 2002; Zalla et al., 2004). Consistent with this, a small fMRI twin study of seven unaffected co-twins, found no difference in neural activity maps during verbal fluency performance. However, this may be due to type II error given the suboptimal sample size for detection of differences in neural activity between groups (Costafreda et al., 2009). Taken together, the majority of behavioural and neuroimaging studies found no consistent verbal fluency impairment in URs.

3.1.10. Executive function

Executive function in URs has been examined extensively in a total of 25 studies. Almost half of studies (k = 12) found executive dysfunction in URs (using TMT-B and the Stroop Colour Word Task (SCWT), whereas the remaining half (k = 13) found no impairment (see Table 1). No consistent pattern of differences in methods, tests, or samples could account for these discrepancies. Despite consistent findings of aberrant neural activity during performance on executive function tests, the direction and location of these changes were conflicting. Specifically, some studies found *increased* activity in the striatum, ventrolateral prefrontal cortex (VLPFC), and interior parietal lobe (Deveney et al., 2012; Kim et al., 2012), while others showed *reduced* superior and inferior parietal activity (with no differences in caudate and VLPFC) (Frangou, 2012). These discrepancies may be due to differences in paradigms used (i.e., the go-no go task and the stop signal task vs. the SCWT) as these tap into disparate aspects of executive function (i.e., response selection vs. response execution). Taken together, behavioural findings have been inconsistent, whereas neuroimaging findings point to aberrant task-related fronto-parietal activity in URs.

3.1.11. Interim summary

Within the 'cold' cognition domains, evidence indicates that the most promising neurocognitive endophenotypes for BD are deficits in verbal memory, problem-solving, and executive function. Despite some degree of variability in behavioural measures of cognition, neuroimaging studies provided relatively consistent evidence for aberrant neural activity in task-relevant neural circuits even when no behavioural differences were identified. Functional neuroimaging measures thus seem to be a more sensitive assay of abnormal brain function than behavioural read-outs.

3.2. 'Hot' cognition

Table 2 displays the 'hot' cognition studies performed in UDs of BD patients. A total of 21 studies investigated 'hot' cognition (Besnier et al., 2009; Brand et al., 2012; Brotman et al., 2014; Brotman et al., 2008a; Brotman et al., 2008b; Dima et al., 2016; Giakoumaki et al., 2010; Green et al., 2011; Hidiroglu et al., 2013; Kanske et al., 2015; Kulkarni et al., 2010; Ladouceur et al., 2013; Linke et al., 2013; Linke et al., 2012; Olsavsky et al., 2012; Pavlickova et al., 2014; Seidel et al., 2012; Sepede et al., 2015; Singh et al., 2014b; Surguladze et al., 2010; Wessa et al., 2015) involving 545 UR and 693 HC participants. Of these, 10 examined only behavioural measures, while 11 also incorporated imaging assessments. The studies explored following aspects of 'hot' cognition: emotion processing and regulation, implicit processing of emotional information, as well as risk-taking, reward and punishment processing (for study details see Table 2).

3.2.1. Emotion processing and regulation

Five studies showed consistent non-specific deficits in the recognition of facial displays of emotion in URs. In particular, unaffected children displayed deficits in the recognition of happiness, sadness, anger, and fear (Brotman et al., 2008a), and required higher emotion intensity to identify those facial expressions (Brotman et al., 2008b). Similarly, adult URs showed general slowing and reduction in accuracy during identification of emotional facial expressions (Seidel et al., 2012). These facial expression recognition problems in URs have been shown to be accompanied by aberrant frontal and/or limbic activation (Brotman et al., 2014; Dima et al., 2016; Olsavsky et al., 2012; Surguladze et al., 2010). Unaffected youths have been shown to exhibit decreased amygdala and inferior frontal gyrus response to angry facial expressions (Brotman et al., 2014) and exaggerated amygdala response to fearful (but not happy) faces (Dima et al., 2016; Olsavsky et al., 2012). In contrast, a study of adult URs showed exaggerated amygdala response to *happy* (but not fearful) faces coupled with increased mPFC reactivity to both happy and fearful faces (Surguladze et al., 2010). Taken together, there is consistent evidence for aberrant fronto-limbic activity to emotional faces in URs. The discrepancy in the *direction* the activity changes may be due to different experimental paradigms across studies (i.e., passive viewing vs. task-directed processing of faces), or could indicate age-related differences in individuals at familial risk for BD.

One fMRI study using emotion-laden picture stimuli reveaked a general blunted startle response in URs, which may indicate aberrant affective reactivity to both pleasant and unpleasant emotional pictures (Giakoumaki et al., 2010). Such abnormal response to emotional pictures is consistent with the demonstration of abnormal neural responses, including *hyper*-activation in insula and *hypo*-activation in parietal cortex to negative emotional picture stimuli (Sepede et al., 2015).

A handful of studies have investigated emotion regulation in URs using behavioural measures (k = 1) and fMRI (k = 1) or self-report measures (k = 2). The studies provide emerging evidence for more 'positive' ratings of positive pictures in URs relative to HCs, and deficient down-regulation of positive emotion during reappraisal of these images (Kanske et al., 2015). They also show *increased* amygdala activity coupled with *reduced* functional coupling between cortico-limbic regions during reappraisal of emotional pictures of either valence (Kanske et al., 2015). These findings corroborate with

the observation of reduced prefrontal top-down control of limbic reactivity to emotional face distracters during a WM paradigm (Ladouceur et al., 2013) and point to deficient cortico-limbic coupling as a marker of genetic risk for BD. On self-report measures of habitual emotion regulation strategies, a large-scale study found abnormally increased engagement in self-blame and rumination in URs (Green et al., 2011), while another study found that URs were less likely to engage in cognitive reappraisal (Kanske et al., 2015).

Taken together, there is emerging evidence for deficits in the recognition of facial expressions and in the ability to dampen emotional response to positively valenced emotional information in URs, which is accompanied by abnormal functional connnectivity between prefrontal and limbic regions. There is also some (albeit very limited) evidence for dysfunctional habitual emotional regulation strategies in URs.

3.2.2. Cognitive interference of emotional stimuli

Two studies found that URs are more easily distracted by task-irrelevant emotional stimuli than HCs (Besnier et al., 2009; Brand et al., 2012). Specifically, in the Emotional Stroop task, they responded slower to depressive-related words (e.g., *sad*, *depressed*) and committed more errors for mania-related words (e.g., *cheerful*, *agitation*) (Besnier et al., 2009), which is indicative of greater emotional distractibility, irrespective of valence. URs also displayed greater obstruction of attentional resources by negatively valenced words in an affective Go-NoGo task (Brand et al., 2012). Taken together, these findings indicate that attentional interference by task-irrelevant emotional stimuli is a promising candidate endophenotype for BD.

3.2.3. Risk-taking, reward and punishment processing

Five studies have found increased risk-taking behaviour in URs (Hidiroglu et al., 2013; Linke et al., 2013; Linke et al., 2012; Singh et al., 2014b; Wessa et al., 2015), whereas **two** studies found no differences (Kulkarni et al., 2010; Pavlickova et al., 2014). These showed lower adjustment scores after losses, suggesting that genetic liability for BD may be linked to a reduced ability to modulate risky activity in the face of certain types of acute stressors (Hidiroglu et al., 2013). At the neural level, white matter integrity in thalamocortical and frontolimbic tracts correlated negatively with risk taking (Linke et al., 2013). Moreover, children at familial risk for BD showed increased orbitofrontal cortex (OFC) activation in response to reward, and decreased pregenual cingulate activation during anticipation of loss on a monetary incentive delay task, which may indicate an increased sensitivity to rewards vs. losses. They also exhibited weaker connectivity between the pregenual cingulate and the VLPFC during reward anticipation, but a stronger connectivity between these regions during anticipation of loss (Singh et al., 2014b). These findings point to deficient top-down regulatory mechanisms during anticipation of reward and excessive emotion regulation during anticipation of losses. Furthermore, URs of BD-I patients show exaggerated activation of the medial OFC in response to reward, punishment, and rule reversal (Linke et al., 2012), and amygdala hyperactivation during rule reversal (Linke et al., 2012). Taken together, these results suggest aberrant frontostriatal activation to reward and losses, which may be a putative neuroimaging endophenotype for BD.

3.2.4. Interim summary

URs exhibit abnormalities at the behavioural and neural levels of emotion processing and regulation, including deficits in the recognition of emotional faces, impaired ability to downregulate positive emotion and a greater attentional interference by emotional stimuli. However, the most consistent evidence for abnormalities in 'hot' cognition is derived from fMRI studies that showed aberrant fronto-limbic activation to different types of emotional stimuli. During reward processing, URs were found to exhibit weaker functional vlPFC-pregenual cingulate connectivity while anticipating rewards, which could underlie a failure to downregulate positive emotion during reward anticipation, although further replication is necessary.

3.3. Neuroimaging

3.3.1. Structural neuroimaging abnormalities

As seen from Table 3, 15 studies including 557 URs and 858 HCs (Bauer et al., 2014; Eker et al., 2014; Frangou, 2012; Frazier et al., 2007; Gunde et al., 2011; Hajek et al., 2015; Hajek et al., 2013; Ladouceur et al., 2008; Linke et al., 2013; Matsuo et al., 2012; Sandoval et al., 2016; Saricicek et al., 2015; Teixeira et al., 2014; Tighe et al., 2012; Versace et al., 2010) analysed structural brain abnormalities in URs; nine reported results for grey matter and eight reported results for white matter (for details see Table 3).

3.3.1.1. Grey matter. Five of the nine studies found reduced grey matter volume in URS compared to HCs in the OFC (Eker et al., 2014; Sandoval et al., 2016), insula (Matsuo et al., 2012; Sandoval et al., 2016), and cerebellum (Eker et al., 2014; Saricicek et al., 2015), respectively. On the contrary, four studies reported *increased* grey matter volume in the dorsolateral prefrontal cortex (DLPFC) (Eker et al., 2014), inferior frontal gyrus (Hajek et al., 2013; Saricicek et al., 2015), insula, and cerebellum (Frangou, 2012) in URs compared to HCs. One study reported increased volume of the parahippocampal gyrus extending into hippocampus in unaffected offspring, but no significant differences in amygdala volume (Ladouceur et al., 2008), whereas another other study found increased volume of the amygdala *but not* hippocampal volumes in unaffected offspring (Bauer et al., 2014). Three studies showed no volume difference in orbitomedial prefrontal cortex (OMPFC), ventromedial prefrontal cortex (VMPFC), or DLPFC (Bauer et al., 2014; Ladouceur et al., 2008; Matsuo et al., 2012). Taken together, the findings regarding grey matter volume were conflicting and inconclusive. We could not identify a consistent pattern of differences in methods or samples that could account for these discrepancies.

3.3.1.2. White matter abnormalities. Of the eight studies, one study found decreased white matter volumes of the right (but not left) medial frontal gyrus in URs (Matsuo et al., 2012). Relatives could be distinguished from HCs in several white matter tracts adjacent to areas involved in the processing of emotions (ventral PFC regions, cingulate gyrus, superior middle temporal gyrus, precuneus, and posterior regions of the occipital lobe) (Hajek et al., 2015). Other studies found bilaterally compromised white matter integrity in the superior longitudinal fasciculus (Frazier et al., 2007), the inferior longitudinal fasciculus, the corpus callosum (Versace et al., 2010), and the internal capsule and unincate fasiculus (Linke et al., 2013). However, two studies found no white matter hyperintensities (WMH) in URs (Gunde et al., 2011; Tighe et al., 2012), despite intermediate volume of WMH relative to HCs and patients with BD (Tighe et al., 2012), and one study showed no white matter abnormalities in any brain regions (Teixeira et al., 2014). This large discrepancy in the results may be due to different diffusion measures (fractional anisotropy, mean, radial or longitudinal −diffusivity; for details see Table 3), as well as the analytic approaches used. Notwithstanding the discrepancies, the findings point to the presence of some local reductions in white matter integrity in URs.

3.3.2. Resting state functional connectivity

Four studies examined functional connectivity during resting state in URs (Li et al., 2015; Lui et al., 2015; Meda et al., 2012; Singh et al., 2014a) (for an overview see Table 3). The most consistent

Table 3
Functional and structural neuroimaging and electrophysiological studies included in systematic review.

Author	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Main Findings
Bauer et al. (2014)	GM volume (Surface based)	sMRI	18 URs, 45 HCs	10.5 (3.4)	50	Offspring	↑ GM volume in the right amygdala. No group differences in GM volume of striatum, caudate, hippocampus, cingulate cortex, temporal regions, fusiform gyrus or PFC
Eker et al. (2014)	GM volume (VBM)	sMRI	28 URs, 30 HCs	34.9 (9.4)	60	Siblings	↓ GM volume in the left orbitofrontal region and right cerebellum, and ↑ GM volume in the left DLPFC
Frangou (2012)	GM volume (VBM)	sMRI	48 URs, 71 HCs	36.5 (13.8)	52	Siblings, offspring	↑ volume of vermis and insula.
Frazier et al. (2007)	FA	DTI	7 URs, 8 HCs	8.9 (3.0)	43	Siblings, offspring	↓ FA bilaterally in the superior longitudinal fasciculus
Giakoumaki et al. (2007)	Acoustic startle reactivity, prepulse inhibition of startle response	EMG	19 URs, 17 HCs	31.6 (7.5)	–	Siblings	↓ prepulse inhibition. No difference between groups in startle reactivity and habituation.
Gunde et al. (2011)	Number of white matter hyperintensities	sMRI	44 URs, 49 HCs	19.8 (3.6)	64	Offspring	No difference in number of white matter hyperintensities
Hajek et al. (2013)[a]	GM volume (VBM)	sMRI	30 URs, 31 HCs	19.5 (3.1)	67	Offspring	↑ right inferior frontal gyrus volume. No other group difference in GM volume.
Hajek et al. (2015)[a]	WM, GM (machine learning)	sMRI	45 URs, 45 HCs	20.1 (3.6)	64	Offspring	URs were distinguished from HCs in bilateral white matter tracts adjacent to the inferior/middle frontal regions, cingulate gyrus, superior/middle temporal gyrus, precuneus, and posterior regions in occipital lobe. No group difference in SVM and GPC for grey matter.
Katsanis et al. (1996)	Visual event related potentials (ERP)	EEG	31 URs, 113 HCs	37.0 (14.6)	48	–	No difference in amplitude, variability and reducing vs. augmentation of N1, P1 and P2.
Ladouceur et al. (2008)	GM volume (VBM)	sMRI	20 URs, 22 HCs	13.0 (2.7)	55	Offspring	↑ volume of left parahippocampal gyri extending into left hippocampus. No group difference in amygdala and orbitomedial PFC volume
Li et al. (2015)	Functional connectivity	rfMRI	20 URs, 20 HCs	40.6 (10.5)	45	Siblings	↑ connectivity between right DLPFC-bilateral amygdala
Linke et al. (2013)	Fractional Anisotrophy (FA), RD and LD	DTI	22 URs, 22 HCs	28.0 (11.0)	50	Siblings, offspring	↓ FA and ↑RD in the right anterior limb of the internal capsule and ↓ FA in the right uncinate fasciculus. No group difference in Corpus Callosum.
Lui et al. (2015)	Amplitude of low frequency fluctuations (ALFF), functional connectivity	rfMRI	28 URs, 59 HCs	37.0 (15.0)	61	–	↑ Functional connectivity between the left precentral/postcentral gyrus and bilateral caudate. No other difference in ALFF abnormalities.
Matsuo et al. (2012)	WM and GM volume (VBM)	sMRI	20 URs, 40 HCs	46.2 (10.7)	75	Mixed	↓ left anterior insular GM volumes and ↓ WM volumes of the right medial frontal gyrus. No group differences in total GM, WM or brain volumes. No group differences in GM volume of VMPFC, DLPFC, ACC, striatum, hippocampus
Meda et al. (2012)	Functional network connectivity	rfMRI	52 URs, 118 HCs	40.6 (13.0)	65	–	↓ connectivity between the Fronto/occipital network and the Anterior default mode/prefrontal network, and between the Meso/paralimbic network and the fronto-temporal/paralimbic network. No difference between the meso/paralimbic and the fronto-temporal/paralimbic networks.

Table 3 (*Continued*)

Author	Paradigm	Measure	*N*	Age	Gender (% female)	UR family status	Main Findings
Pierson et al. (2000)	Event related potentials (ERP). Auditory oddball task, N100, N200, P200, P300, targets and non-targets	EEG	19 URs, 19 HCs	26.2 (6.6)	63	Siblings, offspring	↓ amplitude and longer latency, and a lack of hemispheric dominance of P300, longer latencies of N100 target and lower amplitude for N100 non-target. Behaviourally: ↑ RT and RT-N200 latency in both midline and hemispheres
Sandoval et al. (2016)	GM volume	sMRI	12 URs, 18 HCs	43.4 (19.4)	58	Mixed	↓ right and left PFC, right and left globus pallidum, right and left OFC, right and left insular cortex, left amygdala, right middle temporal gyrus, and total cortex.
Saricicek et al. (2015)	GM volume (VBM)	sMRI	25 URs, 29 HCs	32.1 (11.0)	54	Mixed	↑ left and right interior frontal gyri, left parahippocampal gyrus, left supramarginal gyrus; ↓ cerebellum, vermis
Singh et al. (2014a)	Functional connectivity	rfMRI	24 URs, 25 HCs	12.3 (3.0)	67	Offspring	↑connectivity within the left executive control Network, spec. VLPFC, ↓ connectivities between the left amygdala and pregenual cingulate, between the subgenual cingulate and supplementary motor context, and between the left VLPFC and left caudate. ↑ connectivity between left VLPFC and left superior parietal lobule. No difference in right executive control network, ventral default mode network and default mode network. No differences in connectivity between right amygdala or right VLPFC. URs had a significant decrease of FC between left VLPFC and left caudate with increasing family chaos.
Teixeira et al. (2014)	FA, MD, RD, AD (TBSS)	DTI	18 URs, 20 HCs	12.7 (3.1)	50	Offspring	No difference in FA, MD, RD or AD between groups
Tighe et al. (2012)	Volume of white matter hyperintensities	sMRI	7 URs, 32 HCs				No difference between groups.
Versace et al. (2010)	FA, RD (transverse diffusivity), L1 (Longitudinal diffusivity)	DTI	20 URs, 25 HCs	13.2 (2.5)	45	Offspring	Main group effect:↑ FA and ↓ RD in Corpus Callosum, ↓ RD in right ILF in the temporal lobe and ↑ L1 in right ILF in the visual cortex. Age x group interaction: left corpus callosum showed a decrease of FA with age in URs compared to an increase in FA with age in HC. A nearby region showed an increase of RD with age in URs compared to a decrease of RD with age in HC. ILF in the temporal lobe showed a decrease of RD with age in HCs but no relation of age and RD in URs. Right IFL in the visual cortex showed a decrease of L1 with age in high risk compared to an increase of L1 with age in healthy controls.

Notes: GM = Grey matter; sMRI = Structural Magnetic resonance imaging; fMRI = Functional Magnetic Resonance Imaging; VBM = Voxel-Based Morphometry; FA = Fractional Anisotropy; DTI = Diffusion tensor imaging; WM = White matter; RD = radial diffusion; MD = Mean diffusivity; AD = Axial diffusivity; EMG = Electromyograph; DLPFC = Dorsolateral prefrontal cortex; ALFF = Amplitude of low frequency fluctuations; SVM = support vector machines; GPC = Gaussian process classifiers; VLPFC = Ventrolateral prefrontal cortex; rfMRI = resting state functional MRI; VMPFC = Ventromedial Prefrontal Cortex; FC = Functional Connectivity; ILF = Inferior Longitudinal Fasciculus; TBSS = Tract-Based Spatial Statistics.

[a] Partially overlapping samples.

finding was differences in functional connectivity within regions of the frontostriatal circuitry (Lui et al., 2015; Singh et al., 2014a), although the direction of the abnormalities differed between these studies. In particular, one study showed reduced connectivity between fronto-occipital regions and the anterior default mode-prefrontal network, and between the meso-paralimbic network and fronto-temporal-paralimbic regions (Meda et al., 2012). In contrast, another study found no activity difference within the default mode network (DMN) (Singh et al., 2014a) – a network of medial brain regions that is active during rest and subserves

thought wandering and internal focus (Cha et al., 2014; Raichle and Snyder, 2007). Finally, one study found *increased* connectivity between dlPFC and amygdala bilaterally in URs during resting state (Li et al., 2015). Discrepancies regarding the direction of abnormalities in functional connectivity during resting state may be due to differences in analytic approach (pairwise network comparison vs. functional connectivity within networks and functional connectivity between specific brain regions), and/or age differences between samples across different investigations. Nevertheless, there is relatively consisntent evidence for functional connectivity abnormalities in URs (whether up or down) between brain regions involved in emotion processing and emotion regulation.

3.3.3. Event-related potentials and the startle reflex

Two studies have investigated event related potentials (ERPs) in URs (Katsanis et al., 1996; Pierson et al., 2000) (Table 3). One study found impairment in early as well as later stages of information processing, as reflected longer latency and reduced amplitude of N100 (an ERP measure of attention processes) and P300 (a measure of post-perceptual activity) (Pierson et al., 2000). The studies found no differences in simple visual stimuli processing as reflected by N200 and P200, which is in keeping with the findings in Katsanis et al. (1996). Finally, one study revealed abnormal threat processing in URs as indicated by reduced pre-pulse inhibition of the startle reflex (Giakoumaki et al., 2007).

3.3.4. Interim summary

Structural neuroimaging findings provide emerging evidence for increased amygdala and hippocampus volumes in young offspring of BD patients, but studies are scarce and the findings are inconsistent. Additionally, local reduction in white matter integrity is a relatively consistent finding in URs, although the locations of these changes vary across studies. Finally, a few studies found some evidence for abnormal electrophysiological measures and startle response, which point to abnormalities across different stages of information processing in URs.

4. Discussion

This systematic review identified and included ninety-seven studies the extant findings within 'cold' and 'hot' cognitive function and structural and resting-state neuroimagingn URs compared to HCs in order to identify the most promising endophenotypes for BD.

4.1. 'Cold' and 'hot' cognition

Overall, the most consistent and robust findings across the included literature were within the domains of 'cold' and 'hot' cognition. Studies on 'cold' cognition in healthy URs yielded consistent deficits within the domains of verbal learning and memory, sustained attention, and executive function. Functional MRI studies showed that the impairments in sustained attention and executive function were accompanied by aberrant neural activity in prefrontal, limbic, striatal and parietal regions. Studies on 'hot' cognition in URs showed consistent impairment of facial expression recognition, increased reactivity to emotional stimuli, impaired emotion regulation and increased interference of attentional resources by emotional stimuli. At the neural level, URs exhibited aberrant frontolimbic top-down regulation in to positive and negative stimuli and increased activation in reward processing areas, including the OFC. Fig. 2 provides a wide-angle lens synthesis of the most consistently replicated abnormalities in 'cold' and 'hot' cognition, as well as the underlying neurocircuitries.

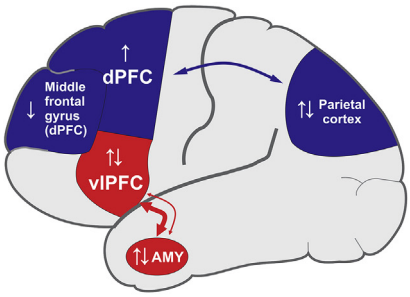
Non-specific neurocognitive impairments within several aspects of 'cold' cognition are well-documented in schizophrenia and unipolar depression (UD) and in their URs (Lee et al., 2014; Rock et al., 2014; Snitz et al., 2006). As such, more pronounced general deficits, with regularly higher effect sizes, are found in relatives of schizophrenic (SC) compared to relatives of individuals with BD (Bora et al., 2009a; Snitz et al., 2006). 'Cold' cognition impairments in URs of patients with BD are therefore unlikely to represent a *specific* endophenotype to BD, but rather appear to represent a broad, transdiagnostic marker of genetic vulnerability to neuropsychiatric illness in general. In contrast, changes in 'hot' cognition, particularly within reward and emotion processing and emotion regulation may represent a more *specific* endophenotype to BD. In particular, aberrant emotion regulation and reward processing implicated in URs of patients with BD have not been shown in individuals at genetic risk for schizophrenia and may thus be a pertinent to mood disorders specifically (Meda et al., 2012). Studies of 'hot' cognition in individuals at genetic risk for UD show relatively consistent presence of *negative* bias (e.g. (Wolfensberger et al., 2008)) and attentional interference by *negative* stimuli (Feder et al., 2011; Joormann et al., 2007), which is accompanied by limbic hyperactivity and hypoactivity in ventral prefrontal regions, similar neural activity patterns in URs of patients with BD (for a review see Miskowiak and Carvalho, 2014). However, the latter group exhibits increased response to and deficient downregulation of emotional responses to *both* negative and positive stimuli. Failure to down-regulate emotional reactivity to *positive* stimuli may thus be an endophenotype that is specific to BD (Rive et al., 2015).

4.2. Structural neuroimaging and resting-state findings

Despite not finding any consistent patterns of grey matter differences, structural neuroimaging studies indicated local reduction in white matter integrity in regions involved in emotion processing and regulation. Resting-state fMRI studies provided consistent evidence for aberrant functional connectivity between frontal and limbic areas, although direction (i.e., up/down) of these abnormalities varied. In sum, neuroimaging findings showed some evidence for structural and resting state abnormalities in areas associated with emotion processing and regulation in URs, but findings were conflicting with regards to the direction and specific location of these changes. Studies reported are in general accordance with research on patients with BD showing functional abnormalities in neural circuits underlying emotion processing and regulation (see Strakowski et al., 2012 for a review). Specifically, aberrant frontal-limbic activation, associated with emotion processing, has been exhibited in patients with BD and persists in periods of remission (Chen et al., 2011b; Phillips and Vieta, 2007).

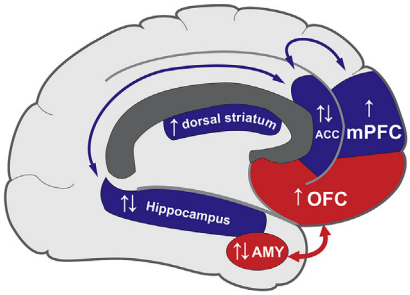
4.3. Limitations and implications

This review provides a 'landscape' view of the studies in URs of BD patients within 'cold' and 'hot' cognition and neuroimaging. The studies included in the present review are cross-sectional, and thus embody a perspective that generally neglects the long-term development of the disorder (Frank et al., 2014). Longitudinal studies of URs are therefore critically needed to provide causal inferences, i.e. to indicate which of the candidate endophenotypes included in this review would predict the development of BD. In addition, the present systematic review included only original peer-reviewed articles. This is a possible methodological limitation because evidence suggests that studies with small sample sizes (which is particularly prevalent in the neuroimaging literature) may be prone to publication bias (Button et al., 2013). However, this systematic review included multiple procedures for identification of articles (i.e., database search and hand-searching of reference lists and tables of contents in the identified articles) thus limiting risk of bias following the PRISMA guidelines. Moreover, findings are difficult



ABNORMALITIES IN COLD COGNITION

- **Deficits in visual learning and memory (of faces)** were associated with increased/decreased activity in hippocampal area, and decreased activity in frontal areas (ACC and middle frontal gyrus)
- **Deficits in working memory** were associated with increased activity in medial and dorsal PFC, and ACC.
- **Deficits in executive function** were associated with increased activity in dorsal striatum (putamen and caudate) and aberrant parietal activity.



ABNORMALITIES IN HOT COGNITION

- **Impaired emotion processing** was associated with increased/decreased frontolimbic connectivity (most consistently vlPFC and amygdala).
- **Impaired emotion regulation** was associated with less PFC top-down regulation of amygdala, and increased positive frontolimbic (amgydala + OFC) connectivity.
- **Impaired reward processing** was associated with increased OFC activity in response to reward.

Fig. 2. Summary of abnormalities in 'cold' and 'hot' cognition in unaffected relatives of bipolar patients.

to compare across studies partly due to different measures used, as well as heterogeneous and often small samples (i.e., relatives of BD-I, BD-II, or both, without differentiation). In addition, although we aimed to exclude studies that provided data from overlapping samples (in these circumstances we considered the report that included the largest dataset), a residual overlapping of samples in different studies might have occurred. Finally, this review is limited by the lack of a guided quality assessment of studies. However, we extracted a wide range of information from included studies, and a critical appraisal of possible methodological limitations of included reports is provided in each section of this systematic review.

The present findings have important implications. The relatively consistent evidence for aberrant behavioural and neuronal measures of 'hot' cognition points to this domain as a putative endophenotype that could be specific for BD. This may inform our understanding of both pathophysiological mechanisms and treatment of BD. Specifically, increased sensitivity to reward and deficient emotion processing and regulation may amplify affect, thereby triggering a spiral into both manic and/or depressive states. As such, deficient prefrontal top-down regulation of limbic reactivity during *positive* emotion processing may represent a predisposition to (hypo)mania (Phillips and Swartz, 2014) and a endophenotype that could be implemented in the clinical assessments to improve future diagnostic discrimination between UD and BD (Cardoso de Almeida and Phillips, 2013; Chase et al., 2013; Pan et al., 2009). Moreover, the findings suggest that emotion dysregulation and aberrant reward processing is associated with genetic liability and may provide key targets for future preventive treatment strategies. Specifically, the individual patient's degree of reward sensitivity and difficulties with positive emotion regulation could potentially support the estimation of their Polarity Index (e.g. depressive vs. manic) (Carvalho et al., 2015) and thereby guide the choice of maintenance therapy.

The identification of endophenotypes that reflect underlying pathophysiological processes may confer risk or resilience toward future onset of BD in at-risk populations. This is vital for the development of novel treatments that specifically target these impairments in patients with BD and individuals at genetic risk. Indeed, preventive emotion-based treatments that aim to improve emotion resilience in at-risk individuals by enhancing their emotional knowledge, –regulation and –utilisation may delay the onset of the disorder or reduce the severity of pathological affective states (see Izard et al., 2008; van Zoonen et al., 2014). These mechanisms may aid the development of targeted psychotherapeutic interventions for the prevention of BD (Pfennig et al., 2014; Vallarino et al., 2015).

5. Conclusion

This review synthesises the extant literature on cognitive function, structural and functional neuroimaging measures in unaffected-first degree relatives of patients with BD compared to HCs. Our findings suggest that abnormalities within 'hot' cognition, specifically aberrant emotion processing and – regulation and reward processing represent the most promising specific endophenotypic marker for BD. Future research is warranted to elucidate the role of 'hot' cognition and associated neural abnormalities as an endophenotype for BD to help improve diagnostic accuracy and develop targeted treatments in at-risk individuals. In addition, the development of novel analytic strategies (e.g., machine learning approaches) may aid the identification of ***multi-modal*** endophenotypes of BD that integrate illness-related changes in neurocognitive *and* neuroimaging measures (Passos et al., 2016).

Conflict of interest

KWM reports having received consultancy fees from Lundbeck and Allergan. MV discloses consultancy fees from Lundbeck, Servier and Astra Zeneca within the last three years. LVK reports having been a consultant for Lundbeck and AstraZeneca within the last 3 years. HLK, IM, JZP, BRC, CAK, and AFC report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.12.011.

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