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Neurocognitive endophenotypes in schizophrenia and bipolar disorder: A systematic review of longitudinal family studies

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ABSTRACT

Although there is substantial evidence supporting the existence of neurocognitive impairment in patients diagnosed with schizophrenia (SZ) and bipolar disorder (BD), few studies have explored the field from an endophenotypic perspective. The present systematic review sought to identify longitudinal family studies exploring suitable neurocognitive endophenotypes in unaffected relatives of patients with SZ and/or BD. Following the PRISMA statement, only five follow-up studies met the inclusion criteria, comprising 79 SZ patients, 159 SZ unaffected relatives of SZ, 131 BD patients, 77 unaffected relatives of BD, and 248 controls. Verbal memory, auditory attention, face memory and emotion processing were found as putative endophenotypic candidates for SZ, whereas this strategy identified none for BD. Substantial heterogeneity and lack of standardization in global neurocognitive assessment within this area should be pointed out; nevertheless, several candidate endophenotypes were identified for SZ, except for executive impairment.

1. Introduction

Currently, there is a wide consensus on the relevance and impact of neurocognitive deficits in schizophrenia (SZ) and bipolar disorder (BD). In SZ, varying degrees of neurocognitive deficits have been described in almost all neurocognitive functions, predominantly memory, attention and executive functioning (Heinrichs and Zakzanis, 1998; Saykin et al., 1994). Although there is global agreement regarding neurocognitive impairment in SZ, trajectories of neuroprogression are still unclear and challenged by controversial findings. Some studies have suggested the stability or even improvement of neurocognitive deficits, especially after a first psychotic episode (Mesholam-Gately et al., 2009; Napal et al., 2012; Szoke et al., 2008).

Research has determined neurocognitive disfunction as a core feature of BD, suggesting a similar cognitive profile as SZ, although to a lesser extent (Solé et al., 2017). In BD, attention, processing speed, executive functions, and verbal memory are described as the most impaired domains (Bortolato et al., 2015; Bourne et al., 2013; Cardoso et al., 2015). Cross-sectional studies suggest progressive cognitive worsening in parallel to a greater number of exacerbations, whereas longitudinal studies mostly indicate the stability of impairment over time (Budde and Schulze, 2014; Samamé et al., 2014). This discrepancy could be related to a mostly short duration of longitudinal studies, and to a high rate of non-completion of follow-up protocols within BD study populations. Significant neurocognitive heterogeneity is also supported by the recent identification of several subtypes or clusters of cognitive functioning in BD patients (Burdick et al., 2014; Jensen et al., 2016; Solé et al., 2016).

Neurocognitive functioning in SZ and BD has been extensively studied, and is currently considered a major predictor of functional outcomes in SZ and BD (Donohoe et al., 2012; Green, 2006; Green et al., 2000; Podogrodzka-Niell and Tyszkowska, 2014). In this context, cognitive heritability and, specifically, the identification of neurocognitive endophenotypes, emerge as a strategic tool in neurocognition, in order to elucidate ethiophysiopathology, and clarify the comprehension

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of such complex genetic disorders. Gottesman and Gould's criteria are commonly accepted for the identification of valid endophenotypes: 1. Association with illness in the population; 2. Heritability; 3. Primarily state independence; 4. Co-segregation of illness and endophenotype within families; 5. Higher frequency in non-affected family members than in the general population (Gottesman and Gould, 2003; Gould and Gottesman, 2006).

Several meta-analyses support the cognitive heritability hypothesis (Blokland et al., 2017), and the identification of neurocognitive impairments and/or putative endophenotypes in unaffected relatives of patients with SZ (Sitskoorn et al., 2004; Snitz et al., 2005; Szöke et al., 2005; Trandafir et al., 2006a; Whyte et al., 2005).

Firstly, Sitskoorn et al. (2004) reviewed 37 articles comprising 1639 unaffected relatives of SZ patients (SZ-Rel) and 1380 healthy controls (HC). Unaffected relatives underperformed HC in several cognitive measures. The largest differences were found on verbal recall memory, visuomotor speed and executive functioning with effect sizes (ES) in the moderate range. ($d = 0.54$, $d = 0.51$). Subsequently, Szöke et al. (2005) meta-analyzed 25 studies in first-degree SZ-Rel, who underperformed HC in all measures analyzed. Small to moderate ($d = 0.26–0.49$) ES were found for Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT) part B, and Stroop Color Word Test (SCWT), whereas ES for phonological and category verbal fluency tests were in the moderate-large range ($d = 0.65$, $d = 0.87$, respectively). Moreover, Snitz et al. (2005) examined 43 neurocognitive variables from 58 studies of 2872 SZ-Rel and 2457 HC. Significant group differences were found in all cognitive domains with small-moderate ES (Moderate ES: continuous performance tasks, auditory verbal learning, design copy tests, category fluency). Differences were persistent even after adjusting group heterogeneity: Trails B for executive functioning ($d = 0.50$), simple and complex continuous performance ($d = 0.56$, $d = 0.60–0.66$, respectively). Finally, global memory performance (Trandafir et al., 2006b) and declarative memory (Whyte et al., 2005) have also been also identified as impaired neurocognitive functions and proposed as putative endophenotypes for SZ based on family studies.

Although the abovementioned family studies in SZ suggest the heritability of neurocognitive deficits, their cross-sectional design in all cases does not allow examine changes or stability (e.g., state versus trait) in SZ-Rel, thus casting doubts about their endophenotypic nature.

Other studies in SZ using longitudinal methodologies do not clearly focus on unaffected relatives, but are referred to the high-risk SZ/psychotic paradigm. These studies aim to investigate cognitive deficits as vulnerability markers predating illness onset, or guiding early intervention strategies in relatives at familial and clinical high-risk, usually adolescent and young adult offspring of patients. The high-risk paradigm has been used in SZ research during the last three decades and recently reviewed (Bora et al., 2014).

Neurocognitive impairment has been also observed in unaffected relatives of BD patients (BD-Rel;Arts et al., 2008; Balanzá-Martínez et al., 2008; Bora et al., 2009; Cardenas et al., 2016). A meta-analysis of 14 studies of BD-Rel, including 7 cognitive functions, reported large ES in the broad domains of verbal memory and executive functions such as working memory, executive control, verbal fluency (Arts et al., 2008). Moreover, Bora et al. (2009) presented a meta-analysis including 18 cognitive variables, comparing performances of BD patients (45 studies, 1446 patients, 1523 controls), first-degree BD-Rel (17 studies, 443 relatives, 797 controls). Small to medium ES were found in most measures of executive functions, verbal memory, sustained attention and psychomotor speed. Response inhibition was suggested as the most suitable endophenotype for BD, with verbal memory and sustained attention proposed as putative candidates (Bora et al., 2009). Recent preliminary evidence suggests the feasibility of neurocognitive clusters also in BD-Rel (Russo et al., 2017).

Studies in SZ and BD combining longitudinal and family designs represent a relevant strategy to identify reliable neurobiological correlates in severe mental disorders. In addition, suitable neurocognitive endophenotypes may have further clinical and therapeutic implications. Therefore, the aim of this review is to investigate whether neurocognitive deficits in SZ and BD patients are also present in their unaffected relatives, analyzing the current longitudinal and family literature, and pointing towards the identification of putative endophenotypes.

2. Materials and methods

The identification of the articles was made through a systematic review, conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) (Moher et al., 2015). Medline/PubMed and PsycINFO/ProQuest were searched in the period between 1980 and February 15th 2018, using the following search terms: schizophrenia OR “bipolar disorder” OR “first episode psychosis” OR “first psychotic episode” cross-referenced with neurocogniti* OR neuropsycholog* OR cogniti* cross-referenced with “first degree” OR relative OR family cross-referenced with follow-up OR longitudinal OR prospective.

Based on previous systematic reviews of longitudinal neuropsychological studies of SZ patients (Rund, 1998), a minimum of 1-year follow-up was considered for inclusion of candidate studies. Follow-up studies had to include at least two neuropsychological assessments tapping specific cognitive functions or domains in unaffected relatives of subjects diagnosed with SZ or BD and healthy controls.

High-risk (HR) participants were excluded from this review, since the identification of cognitive vulnerability markers of transition to psychosis was not the aim of this study.

Other exclusion criteria were follow-up periods under 1 year, IQ indexes as a single neuropsychological assessment and multiple publications including the same data.

Two researchers (SCL and VBM) independently examined the titles and abstracts of the retrieved studies to identify those fulfilling selection criteria. The selected articles were subsequently examined on their full-text version. Additional candidates were obtained from reference lists provided by the articles. Each article was rated with the Newcastle-Ottawa Quality Assessment Scale (NOQAS) to evaluate the risk of bias and quality of the study.

3. Results

A total of 804 hits were retrieved from the databases (549 in Pubmed, 255 in PsycINFO) as potential papers for inclusion (Fig. 1). After removing 183 duplicated articles, 621 articles were screened; reasons for exclusion and magnitudes in each case are detailed in Fig. 1. Finally, 54 articles were full-text assessed for eligibility.

Only five follow-up studies met the selection criteria, comprising 79 SZ patients, 159 SZ-Rel, 131 BD patients, 77 BD-Rel and 248 HC. The studies included in this systematic review and their findings are presented below in chronological order. For further details about the articles included, major characteristics, neurocognitive batteries and performance, see Table 1.

Based on a previous sample of 38 chronic, severe and institutionalized SZ patients, Faraone et al. (1999) aimed to demonstrate in a subsequent four-year follow-up study, the stability of neuropsychological deficits in 39 first-degree SZ-Rel (siblings, parents and offspring) compared to 45 HC. The neurocognitive battery assessed the patterns of executive functioning, verbal memory, visual memory and auditory attention. Delayed alternation (DA) and object alternation (OA) were other executive measures used for memory assessment, although they were only added at the 4-year follow-up. Significant differences were found in neurocognitive performance for IVM, DVM, IVR, DVR between relatives and HC in regards to gender, with more pronounced differences for women; although no significant differences were found for OA and DA. Generalized Estimating Equations model (GEE) was used to compare SZ-Rel and HC, modeling each test score as a function of

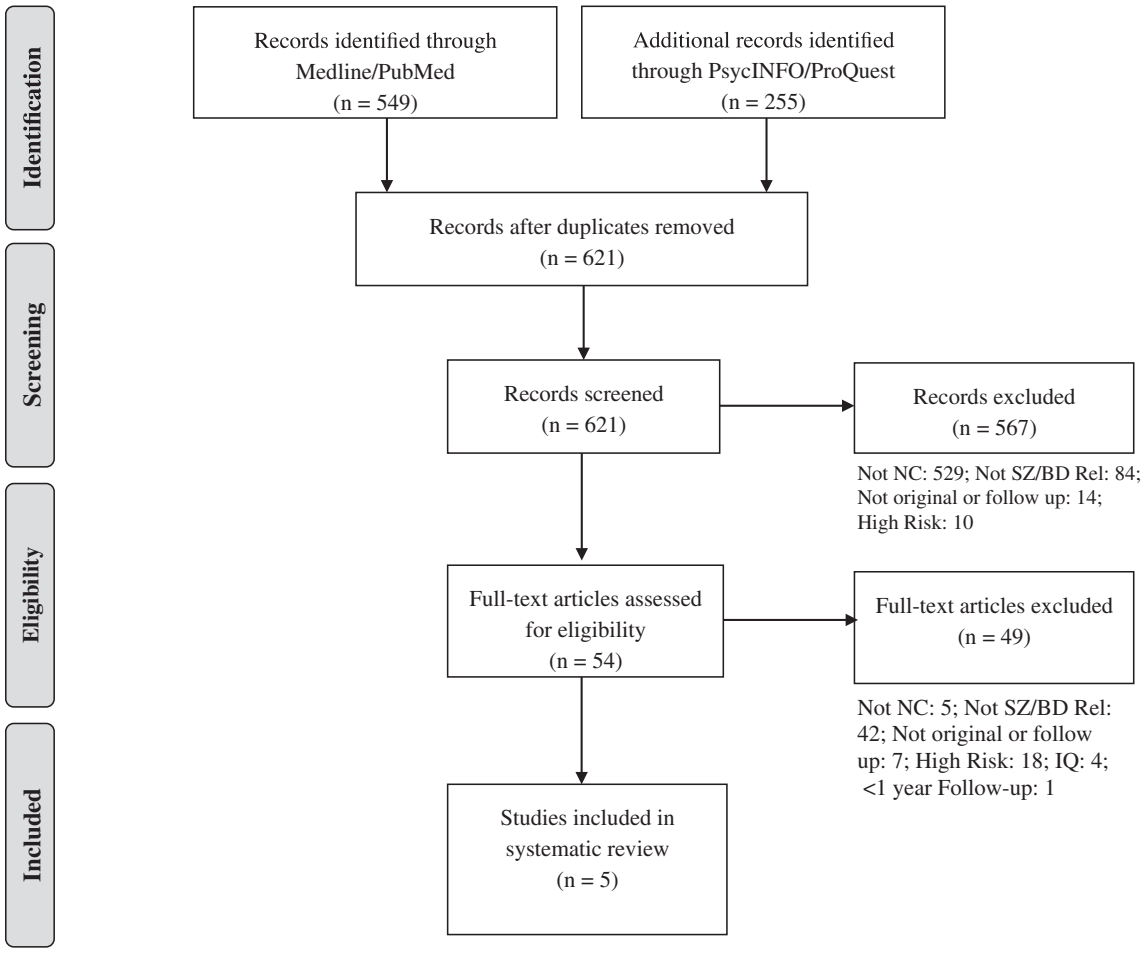

Fig. 1. PRISMA diagram describing process of guideline selection. NC: Neurocognitive studies; SZ/BD Rel: Schizophrenia or bipolar disorder relatives' studies; IQ: Intelligence quotient as single neurocognitive measure.

group, time, gender and interactions. Besides, the Intraclass Correlation Coefficient (ICC) was used for assessing stability over time. The authors found significant differences in all variables at baseline. However, follow-up analysis revealed a persistent deficit only in IVM, DVM and DLDD among SZ-Rel. Additionally, improvement in WCST-CAT and WCST-TP is reported in the analysis of HC performance, with no statistical differences at follow-up. In terms of stability, variances tended to decrease over time while ICC demonstrated not remarkably high level of significance in almost all measures, except for IVM in SZ-Rel. Relatives showed greater variability than controls for WCST-CAT and IVM.

A subsequent 13-month follow-up study (Wittorf et al., 2004) compared 11 Schizophrenia (SZ) and Schizoaffective Disorder (SZA) patients, 21 unaffected first-degree relatives (parents, siblings, offspring), and 21 HC. The composition of families was simplex. The neurocognitive battery applied to all participants was composed by a factorization of neurocognitive measures into five groups: 1. Vigilance, attention, psychomotor (VAP); 2. Secondary verbal memory (SVM); 3. Immediate and working memory (IWM); 4. Abstraction and problem solving (APS); and 5. Rey complex figure test (RCFT). Neurocognitive domains assessed included executive functioning, attention, visual memory, visuospatial ability, memory and processing, processing speed, verbal fluency, auditory verbal memory. In patients, neurocognitive performances on SVM and VAP were found to be associated with scores on the negative and disorganized syndromes, respectively. No correlation was found for other clinical variables, including age at onset, illness duration and positive symptoms. At baseline, SVM was the most impaired domain in relatives and patients (HC > SZ-Rel > SZ), while severe impairment was also found in the VAP domain (HC > SZ-Rel > SZ) and RCFT (SZ, SZ-Rel < HC). No significant differences were found among the three groups in APS. At follow-up, patients improved performance in almost all domains within ±0.5 SD of normative level, maintaining low performance on SVM (within ±1 SD below normative level). Unaffected relatives improved on VAP and RCFT, thereby equalizing SZ and HC performance, although no significant differences were found among SZ, Rel and HC. In sum, SVM was the only persistently impaired domain at baseline and follow-up.

Another five-year follow-up study compared 34 SZ/Schizoaffective (SZA) patients from multiplex families, 65 first- or second-degree relatives, and 45 HC (Roalf et al., 2013). In order to assess longitudinal neurocognitive performances, the authors used the traditional mean performance and the across-task measure of Intra-individual variability (IIV), which is an innovative approach for the detection of changes over time. Several domains composed the employed Computerized Neurocognitive Battery (CNB): Abstraction and mental flexibility, attention, verbal memory, face memory, spatial memory, language reasoning, sensorimotor processing speed, emotion processing. Moreover, IQ was estimated by means of the Wide Range Achievement test (WRAT 3). Analysis of performance was made in terms of accuracy and speed. The interaction between clinical or sociodemographic variables and neurocognitive performance was not assessed in this study. SZ patients showed pervasive deficits across all domains. It is remarkable that SZ-Rel performed in an intermediate level, at both assessments. Regarding accuracy, SZ-Rel underperformed controls in FMEM at both assessments, with additional deficits in LAN at follow-up. FMEM was the only persistently impaired domain in SZ-Rel. Regarding speed, baseline performance of SZ-Rel was significantly worse than that of HC in LAN

Table 1
Major characteristics and neurocognitive performance of the selected articles.

Reference	Country	Follow-up	Sample	Instruments	Major Results	Comments
Faraone SV, Seidman LJ, Toomey R, Kremen W, Pepple J, 1999	USA	4 years	Rel=39 HC=45	Clinical interview, no scale application. Reading ability: WRAT-R- reading. **Neurocognitive battery:** Executive functioning (ExF): - WCST categories (CAT) - WCST total perseverations (TP) -Only follow-up: DA- Delayed alternation; OA - Object alternation. Verbal Memory: WMS-R - IVM, DVM Visual Memory: WMS-R - IVR, DVR Auditory Attention: - DLDD	**Baseline** / **Follow-up** Rel<HC All measures / Rel<HC **IVM** **DVM** **DLDD** Rel=HC WCST CAT WCST TP ICC Significance: all except IVM (R). - [Group] (R<C): IVM, DVM, DLDD - [Time]: WCST-CAT, WCST PE - [Group x time] = None (Stability) Variability: R>C: WCST, IVM	Sample: 1. SZ 2. Heterogeneous: siblings, parents, adult children (1st degree, age range[18-59]) 3. Excludes substance abuse (last 6 months), neurological impairment, intellectual disability, in Rel and HC. 4. Psychotropic treatment (Rel, HC): no data. Neuropsychological battery: - False positive of practice effect: WCST - Addition of OA, DA only in follow-up. Reliability of changes: ICC - Low stability coefficients.
Wittorf A, Klingberg S, Wiedemann G, 2004.	Germany	13 months	SZ=11 Rel=21 HC=21	**Clinical symptom assessment:** PANSS (PS, NS); DS **Neurocognitive battery** **Varimax factorization:** F1. VAP - ds CPT: SNS, RT. - Benton test: Number correct (NC), Total errors (TE) - TMT: TMT-A, TMT-B, Δ [B-A] - Digit-symbol F2. SVM - AVLT: T1, T5, [1-5], T7d F3. IWM - Digit-span: Total, forward (FW), backward (BW), [FW-BW]. F4. APS - WCST: Trials, PE, CAT F5. RCFT	**Baseline** / **Follow-up** SZ<Rel<HC VAP; SVM / Rel, SZ<HC **SVM** DVM DLDD SZ,R<C RCFT SZ=Rel=HC APS / SZ=Rel=HC VAP RCFT SZ<HC IWM / SZ<HC None SZ=HC None / SZ=HC IWM APS [Time]: All (VAP, IWM, APS, RCFT, SVM) [Group]: All except SVM [Time x Group]: All except IWM.	Sample: 1. SZ, SZA 2. Includes 1st episode cases (almost 50%) 3. Simplex families 4. Includes 1st degree relatives, age range [16-69] 5. Excludes substance abuse (last 1 month), neurological impairment, IQ <80, in Rel and HC. 6. Excludes psychotropic treatment (Rel, HC). Neuropsychological battery: - Possible practice effect. Reliability of changes: - NO - Statistics: No correction for multiple testing.

Table 1 (*continued*)

<table>
<tr>
<td>Roalf D, Gur RB, Almasy L, Richard J, Gallagher RS, Prasad K, Wood J, et al, 2013</td>
<td>USA</td>
<td>5 years</td>
<td>SZ= 34
Rel= 65
HC= 45</td>
<td>Global Functioning: GAF
Negative Symptoms: SANS
Positive Symptoms: SAPS
IQ: WRAT 3

<u>Computerized neurocognitive battery (CNB)</u>

- Abstraction and mental flexibility (ABF)
- Attention (ATT)
- Verbal memory (VMEM)
- Face memory (FMEM)
- Spatial memory (SMEM)
- Language reasoning (LAN)
- Sensorimotor processing speed (SMPS)
- Emotion processing (EMO)</td>
<td>
<table>
<tr><th>Accuracy Baseline</th><th>Accuracy Follow up</th></tr>
<tr><td>HC,Rel>SZ
All measures</td><td>HC,Rel>SZ
All measures</td></tr>
<tr><td>HC>Rel
FMEM</td><td>HC>Rel
FMEM
LAN</td></tr>
<tr><td>HC=R
All except FMEM</td><td>HC=Rel
All except FMEM, LAN</td></tr>
<tr><th>Speed Baseline</th><th>Speed follow up</th></tr>
<tr><td>HC>SZ
ABF
ATT
VMEM
SMPS
EMO</td><td>HC>SZ
All except LAN</td></tr>
<tr><td>Rel>SZ
ABF
ATT
VMEM
SMPS</td><td>Rel>SZ
All except SMEM</td></tr>
<tr><td>HC>Rel
LAN
EMO</td><td>HC>Rel
SMPS; EMO; FMEM;
SMEM</td></tr>
</table>
ICC: ↑ in most domains

<u>Stability of Mean performance over time:</u>

<table>
<tr><th>Accuracy</th></tr>
<tr><td>C: Stable (>), ↑FMEM</td></tr>
<tr><td>R: Stable (>), ↑ATT, ↑ABF, ↑<u>FMEM</u></td></tr>
<tr><td>P: Stable in all</td></tr>
<tr><th>Speed</th></tr>
<tr><td>C: Stable (>), ↓VMEM</td></tr>
<tr><td>R: Stable <u>(EMO),</u> ↓FMEM ↓VMEM</td></tr>
<tr><td>P: Stable (ATT, LAN, ABF, SMEM, EMO)
↓ FMEM, ↓VMEM ↓SMP</td></tr>
</table>
</td>
<td>Sample:
1. SZ, SZA
2. Homogeneous: only Caucasian families
3. Heterogeneous: multiplex families (≥10 affected family members.
4. Includes 1st and/or 2nd degree relatives, [15-?]
5. Excludes substance abuse (Urine testing), IQ<70, only in R.
6. Excludes any CNS disorder hindering performance. Primary medical illness causing impairment: no data.
7. Psychotropic medication in R and C: no data.

Neuropsychological battery:
- Possible practice effect

Reliability of changes over time:
1. Test retest (ICC)
2. Mean performance (z-score)
3. IIV</td>
</tr>
</table>

(*continued on next page*)

<table>
<tr>
<td>Sánchez-Torres AM, Basterra V, Moreno-Izco L, Rosa A, Fañañás l, Zarzuela A, et al, 2013.</td>
<td>Spain</td>
<td>10 years</td>
<td>SZ=34
Rel=34
HC=13</td>
<td>Clinical Interview: CASH
Toxic abuse: CIDI

<u>Neurocognitive battery:</u>
<u>Executive functioning:</u>
- TMT-B
- WCST-64
- Categories (CAT)
- Total errors (TE)
- Perseverative errors (PE)
- Conceptual level responses (CLR)
- Failure to maintain set (FMS)</td>
<td>
<table>
<tr><th>Baseline</th><th>Follow-up</th></tr>
<tr><td>Rel=HC
All measures</td><td>Rel=HC
All except WCST TE</td></tr>
<tr><td>Rel<HC
None</td><td>Rel<HC
WCST TE</td></tr>
<tr><td>Rel>SZ
TMT-B
WCST CAT</td><td>Rel>SZ
All except WCST FMS</td></tr>
<tr><td>HC>SZ
TMT-B,
WCST CAT, TE</td><td>HC>SZ
TMT-B
WCST CAT</td></tr>
</table>
<u>SZ ≠ Rel ≠ HC:</u>
- [Group]: TMT-B, WCST (except FMS)
- [Group x time]: TMT-B
<u>RCI, CSC:</u>
- (SZ,Rel): Tendency to stability pattern
- TMT-B, WCST
</td>
<td>Sample:
1. SSD (SZ, SZA, Psychotic mood disorder)
2. Homogeneous: only siblings (1st degree, age range [14-41])
3. Excludes substance abuse or any drug treatment, only in C.
3. Substance abuse or dependence, neurological impairment, intellectual disability, psychotropic treatment, in R and C: no data.

Neuropsychological battery:
1. Brief
2. Reduced possibility of practice effect.

Reliability of changes over time:
1. RCI (Reliable Change Index)
2. CSC (Clinically Significant Change)</td>
</tr>
<tr>
<td>Correa-Ghisays P, Balanzá-Martínez V, Selva-Vera G, Vila-Francés J, Soria-Olivas E, Vivas-Lalinde J, et al, 2017.</td>
<td>Spain</td>
<td>5 years</td>
<td>BD= 131
Rel= 77
HC= 83</td>
<td>IQ: WAISS III

<u>Manual motor skills:</u>
- Finger tapping test</td>
<td>
<table>
<tr><th>Baseline</th><th>Follow-up T1</th><th>Follow-up T2</th></tr>
<tr><td>HC,Rel>BD</td><td>HC>BD</td><td>HC>BD</td></tr>
<tr><td>Rel=HC</td><td>Rel=HC</td><td>Rel=HC</td></tr>
</table>
</td>
<td>Sample:
1. BD
2. Homogeneous: right and both handed.
3. Includes 1st degree R (parents, siblings, offspring), age range [18-78]
5. Excludes substance abuse, IQ<70, head trauma, motor dysfunctions and neurological or medical conditions, only in patients.
6. Psychotropic medication in Rel, HC: no data.

Neuropsychological battery:
- Corrected practice effect

Reliability of changes over time:
- Square regression adjustment</td>
</tr>
</table>

Note: SZ: Schizophrenia Patients; BD: Bipolar Disorder Patients; SZA: Schizoaffective Disorder; Rel: Relatives; HC: Healthy Controls; WCST: Wisconsin Card Sorting Test; WRAT-R: Wide Range Achievement Test; WMS-R: Wechsler Memory Scale; IVM: Immediate Verbal Memory; DVM: Delayed Verbal Memory; IVR: Immediate Visual Reproductions; DVR: Delayed Visual Reproductions; DLDD: Dichotic Listening Digits Detected; PANSS: Positive and Negative Syndrome Scale; PS: Positive Syndrome; NS: Negative Syndrome; DS: Disorganization Scale; VAP: Vigilance, Attention, Psychomotor; SVM: Secondary Verbal Memory; IWM: Immediate Working Memory; APS: Abstraction and Problem Solving; RCFT: Rey Complex Figure Test; ds CPT: Degraded Stimulus Continuous Performance Test; SNS: Sensitivity; RT: Reaction time; AVLT: Auditory Verbal Learning Test; T1: Trial 1; T5: trial 5; T7d: trial 7-delay; TMT: Trail Making Test; CASH: Comprehensive assessment of Symptoms and History (CASH –Andreasen et al., 1992); CIDI: Structured Interview (patients and relatives) based on the Composite International Diagnostic Interview (CIDI – WHO, 1993); WAISS III: Wechsler Adult Intelligence.

and EMO domains. Nevertheless, deficits in SMPS, FMEM, SMEM and EMO were observed at follow-up, and EMO was the only persistently impaired domain over time in SZ-Rel. Reliability of changes over time was confirmed by high ICC in most domains. The stability of performance was assessed by mean performance (even if regarding accuracy non persistent deficit was observed in FMEM, regarding speed the deficit was persistent in EMO), and analysis of the across-task variability (suggesting relatives as the only group to maintain underperformance in accuracy and speed).

Moreover, a ten-year follow-up study compared executive performance of 34 patients diagnosed with Schizophrenic Spectrum Disorder (SSD), 34 of their unaffected siblings and 13 HC (Sánchez-Torres et al., 2013). SSD included SZ, SZA and psychotic mood disorders. Only two neurocognitive tasks were used: Trail Making Test B (TMT—B) and the Wisconsin Card Sorting Card Test (WCST-64). The variables gender, age, and substance use, did not show significant association on the neurocognitive performance for executive functions. At baseline, SZ-Rel showed better performance than patients on TMT-B and WCST categories, but no significant differences with HC. At follow up, relatives overperformed patients in all measures except for WCST- FMS, and underperformed controls in WCST-TE. A global tendency to stability in both TMT-B and WCST categories was confirmed by RCI (Reliable Change Index) and CSC (Clinically Significant Change), statistical features used to estimate changes in executive tests and clinical meaning of change over time. In sum, no persistent neurocognitive deficits over time were identified when comparing relatives and controls.

Finally, only one longitudinal, family study has examined potential neurocognitive endophenotypes in BD. This five-year, follow-up study assessed 131 euthymic BD patients, 77 BD-Rel and 83 HC (Correa-Ghisays et al., 2017). The aim of the study was to examine manual motor speed as a putative endophenotype using the Finger-Tapping test (FTT) as a single variable. Sociodemographic and clinical characteristics of the sample were analyzed using ANCOVA, except family and age, whose influence was removed using a linear regression. Inverse linear correlation between FTT values and age was adjusted using a square regression adjustment, correcting simultaneously time and learning effect. Groups were compared using a Tukey multiple-comparison of means, and potential confounders examined with an ANOVA test for the first assessment of each participant. Gender was significantly associated with neurocognitive performance, with men performing better than women at baseline. Moreover, performance on the FTT decreased more with age only among BD patients, but not in their relatives and controls. The performance of BD-Rel on motor speed was intermediate to that of patients and HC, both in FTT total values and all subtests, no stable deficit was identified in BD-Rel. Table 2 synthesizes the assessed functions and domains in this review.

Table 2
Neuropsychological assessment of test and domains.

Test and variables	Cognitive domains
TMT-B	Visuomotor speed
- [B-A]	Executive functions,
WCST	Abstraction
- CAT, Trials, TE, PE, TP, CLR, FMS	Concept formation
Digit span	Executive functions
- Total, forward (FW), backward (BW), [FW-BW].	Working memory
IVM	Verbal memory
DVM	
AVLT	
- T1, T5, [1–5], T7d	
IVR	Inmediate and delayed
DVR	visual/visuospatial memory
Benton test	
- NC, TE	
RCFT	
DVR	
DLDD	Attention
CPT	
- SNS, RT.	
Digit span FW-BW	
TMT-A	Visuomotor tracking
RCFT	Visuospatial processing
- Delayed recall	Processing speed
Verbal Fluency	Language function
- Number words	Processing speed
Digit symbol	Working memory
	Psychomotor
Finger Tapping Test	Motor function, speed and control
	Attention, coordination

Note: TMT: Trail Making Test; WCST: Wisconsin Card Sorting Test; CAT: Categories Achieved; TE: Total errors; PE: Perseverative Errors; TP: Total Perseverations; CLR: Conceptual Level Responses; FMS: Failure to Maintain Set; IVM: Immediate Verbal Memory; DVM: Delayed Verbal Memory; AVLT: Auditory Verbal Learning Test; T1: Trial 1; T5: trial 5; T7d: trial 7-delay; IVR: Immediate Visual Reproductions; DVR: Delayed Visual Reproductions; NC: Number Correct; RCFT: Rey Complex Figure Test; DLDD: Dichotic Listening Digits Detected; CPT: Degraded Stimulus Continuous Performance Test; SNS: Sensitivity; RT: Reaction time.

4. Discussion

This is the first systematic review of neurocognitive endophenotypes in SZ and BD based on longitudinal, family studies. Our results show the scarcity of extant longitudinal studies of unaffected relatives of SZ/SSD or BD patients, since only five follow-up studies met the selection criteria. These limited findings may cast doubt regarding the restrictive criteria and the exclusion of HR subjects. As mentioned, the identification of cognitive vulnerability markers of transition was not the aim of this study.

Overall, the neurocognitive performance of unaffected relatives was intermediate to that of patients and HC, which concurs with previous cross-sectional, family studies (Sitskoorn et al., 2004; Snitz et al., 2005; Szöke et al., 2005; Trandafir et al., 2006a; Whyte et al., 2005). The longitudinal, family perspective here analyzed showed the persistence of deficits also in relatives, further confirming the endophenotypic nature of neurocognitive impairments.

Based on this approach, four neurocognitive endophenotypic candidates were identified for SZ: verbal memory (Faraone et al., 1999; Wittorf et al., 2004), auditory attention (Faraone et al., 1999), face memory (Roalf et al., 2013) and emotion processing (Roalf et al., 2013). No putative endophenotype candidate in longitudinal studies was identified for BD. Verbal memory (Sitskoorn et al., 2004) was the only putative endophenotype identified by this review as fully concordant with previous meta-analyses of cross-sectional studies of unaffected relatives of SZ. Conversely, our current findings, based on the longitudinal, family approach do not support executive functioning as a putative endophenotype of SZ, as suggested in meta-analyses of cross-sectional family studies (Sitskoorn et al., 2004; Snitz et al., 2005; Szöke et al., 2005).

On the other hand the lack of identification of neurocognitive endophenotypes in BD is also discordant with previous meta-analysis of cross-sectional methodologies (Arts et al., 2008; Bora et al., 2009). Nevertheless, the small number of studies may explain such inconsistency, and therefore identifies a gap in neurocognitive research.

Important differences between the studies in this review were found, regarding sample characteristics, periods of follow-up, neurocognitive batteries, and statistical approaches.

First, regarding *sample features,* its size was relatively small in all of the studies. Some studies distinguished between simplex (Wittorf et al., 2004) and multiplex families (Roalf et al., 2013). This categorization strategy may be useful to discriminate the degree of genetic loading, which outlines the sample homogeneity and highlights the degree of consanguinity as a major direct risk marker. Only first-degree relatives were recruited in four studies (Correa-Ghisays et al., 2017; Faraone et al., 1999; Sánchez-Torres et al., 2013; Wittorf et al., 2004), whereas first- and second-degree relatives were examined in the remaining study (Roalf et al., 2013). Overall, the age of relatives ranged from 14 to 78 years, while its composition was globally heterogeneous,

basically in regards to the definition of SSD variable, which differs between studies. The SSD group was composed by SZ and SZA in two studies (Roalf et al., 2013; Wittorf et al., 2004), whereas psychotic mood disorders were considered as part of the SSD in another study (Sánchez-Torres et al., 2013). Parameters with a likely influence in neurocognitive performance were heterogeneously taken into account, such as substance abuse, concomitant psychotropic medication, primary or secondary central disease or damage hintering neurological performance, and intellectual disability. Interestingly, most authors studied interactions between sociodemographic or clinical variables, and neurocognitive performance (Correa-Ghisays et al., 2017; Faraone et al., 1999; Sánchez-Torres et al., 2013; Wittorf et al., 2004). Opposite associations between gender and neuropsychological performance have been described (Correa-Ghisays et al., 2017; Faraone et al., 1999). Length of *follow-up* ranged from 13 months (Wittorf et al., 2004) to 10 years (Sánchez-Torres et al., 2013). The *neuropsychological assessment*, reflected on neurocognitive batteries selection, was based on the literature (Correa-Ghisays et al., 2017; Roalf et al., 2013; Wittorf et al., 2004), based on previous data analysis in relatives and HC (Faraone et al., 1999), or restricted to the executive domain (Sánchez-Torres et al., 2013). Although the search was not restricted to basic neurocognition, only one study identified emotional processing as a measure of social cognition (Roalf et al., 2013). Moreover, different approaches were used to measure the *reliability of changes* over time: RCI and CSS (Sánchez-Torres et al., 2013), ICC (Faraone et al., 1999; Roalf et al., 2013), a specific across intra-individual variability measure (Roalf et al., 2013) or square regression adjustment (Correa-Ghisays et al., 2017). The management of ceiling effect was identified in most of the studies. Nevertheless none applied correction for multiple testing. Besides, some statistical strategy potentially reducing statistical power was identified (Faraone et al., 1999). Moreover, lack of sample size calculation may render all studies underpowered to detect significant differences and false negative results (e.g., type II error) cannot be ruled out.

The remarkable between-study heterogeneity may limit the global reliability of findings and the identification of candidate endophenotypes based on longitudinal, family studies. Future research would benefit from the application of standardized definitions, inclusion criteria and methodologies for reducing heterogeneity, even if general guidance is nowadays limited (Lorenc et al., 2016). Future family studies may also benefit from the combined use of biomarkers, neuroimaging and neurocognitive data (Isaac and Januel, 2016; Kapczinski et al., 2014; Miskowiak et al., 2017; Tatay-Manteiga et al., 2017).

Despite these limitations and the scarcity of literature, preliminary evidence so far analyzed may be used as a standing point to build upon the identification of suitable neurocognitive endophenotypes in severe mental disorders. In turn, this might allow reaching more ambitious goals in recovery-oriented clinical practice. Early detection, preventive and therapeutic interventions targetting neurocognition (Miskowiak et al., 2016; Torrent et al., 2013) have been suggested to improve functional outcomes and quality of life in SZ and BD patients (Bonnin et al., 2016; Vinogradov and Schulz, 2016) as well as in their unaffected relatives (Gkintoni et al., 2017; Jabben et al., 2010; Scala et al., 2012), and possibly symptom-mediated (Jabben et al., 2010; Scala et al., 2012), or characterized across the psychosis continuum (Gkintoni et al., 2017).

Accordingly, clinical staging models of SZ and BD include at-risk relatives, mainly offspring, as candidates for non-invasive or preventive interventions (Fusar-Poli et al., 2017; Grande et al., 2016; Vieta et al., 2018). Moreover, the concept of cognitive reserve has emerged as a significant mediator of cognitive impairment (Amoretti et al., 2016; de la Serna et al., 2013; Grande et al., 2017) and perhaps a potential endophenotype. Unfortunately, no studies analyzing neurocognitive measures and functional recovery in unaffected relatives have followed a longitudinal perspective and there are only a few cohorts of at risk subjects between gender and neuropsychological performance being prospectively followed for conversion and neuropsychological outcome.

In sum, current findings are heterogeneous, susceptible to bias, and should be considered as tentative results; nevertheless, they highly suggest the endophenotypic nature of persistent neurocognitive dysfunction in SZ unaffected relatives, based on longitudinal family studies. The identification of putative neurocognitive endophenotypes by means of this strategy may serve as a tool for early intervention and therapeutic target in SZ and according to literature, especially in the case of BD. Further research is clearly warranted in this area.

Contributors

SCL wrote the first draft of the paper and contributed to literature research, analyses and interpretation. VBM contributed to the analysis of literature and critical review of the article. RTS, LL, EV and MJC contributed substantially to analysis, interpretation and writing of the manuscript. All authors have given final approval of the manuscript.

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Declaration of Competing Interest

None.

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