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Neuropsychological correlates of schizotypy: a systematic review and meta-analysis of cross-sectional studies

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ABSTRACT

Introduction: Cognitive deficits can precede the onset of psychotic episodes and predict the onset of the illness in individuals with schizotypy traits. In some studies, high levels of schizotypy were associated with impairments in memory, attention, executive functions, and verbal fluency. This review provides a more comprehensive understanding of cognitive impairments related to schizoytpy.

Methods: A systematic review of "schizotypy and neuropsychological measures" was conducted, and it retrieved 67 studies. All papers with case-control design showing means and standard deviations from neuropsychological measures were included in a metaanalysis (n = 40). A comparison between our finding and another metaanalysis with patients with schizophrenia-spectrum disorders [Fatouros-Bergman, H., Cervenka, S., Flyckt, L., Edman, G., & Farde, L. (2014). Meta-analysis of cognitive performance in drugnaive patients with schizophrenia. Schizophrenia Research. doi:10.1016/j.schres.2014.06.034] was performed to study the similarities on the MATRICS domains between the two disorders.

Results: We found evidence of worse functioning of verbal and visual-spatial working memory, and of language in people with schizotypy or with schizotypal traits. Working memory deficit is present in both schizotypy and schizophrenia with larger effect sizes compared to other domains.

Conclusions: Working memory deficit might be a cognitive marker of the risk of psychosis. Interventions targeting cognitive deficits early may be crucial to the prevention of psychosis.

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Introduction

Schizotypy refers to a latent personality construct that indicates an individual's proneness to psychosis/schizophrenia. The term "schizotype" (from "schizophrenic genotype") was used to describe individuals who, despite having no psychosis, displayed attenuated symptoms that were phenotypically similar to those observed in schizophrenia (Rado, 1953).

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The term has spread to indicate a schizophrenia-like pattern of beliefs and perceptual experiences observed in first-degree relatives of patients diagnosed with psychosis, and in people from the general population in the absence of psychosis (Tarbox & Pogue-Geile, 2011). Schizotypy is conceived as a major vulnerability factor for schizophrenia (Barrantes-Vidal, Grant, & Kwapil, 2015).

The schizophrenia-like pattern of beliefs and perceptual experiences underlying schizotypy has been formalised into a personality disorder. According to DSM-5 criteria, the schizotypal personality disorder is characterised by a specific pattern of social and interpersonal relations, reduced capacity for close relationships, as well as cognitive or perceptual distortions and eccentricities of behaviour beginning in early adulthood and emerging in a variety of contexts (American Psychiatric Association, 2013). The schizotypal personality disorder may represent a risk of developing schizophrenia-spectrum disorders (Debbané & Barrantes-Vidal, 2015).

The focus on the early detection and intervention in psychosis (Birchwood, Todd, & Jackson, 1998; McGlashan, 1996; McGorry, 2015) has renewed interest in the assessment of vulnerability traits for psychosis (Fonseca-Pedrero et al., 2008; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; Stefanis et al., 2004). The investigation of these vulnerability traits in the general population is an important strategy to identify genes potentially related to psychosis, and to study correlates of psychosis-proneness without the interference of medications and other confounding factors (e.g., the negative impact of institutionalisation on cognition), which may bias the identification of the psychosis correlates.

The dimensional model of schizotypy postulates that the degree of schizotypal traits varies on a continuum between two extremes, from normality all the way through to schizophrenia, with clinical schizotypy in the middle (van Os et al., 2009). The observation of subclinical schizotypal traits and individual psychotic symptoms in the general population has further supported the concept of schizophrenia spectrum disorders (Rawlings, Williams, Haslam, & Claridge, 2008).

Generally, schizotypy is assessed by interviews and self-reported questionnaires.

Subjects who had high scores in the self-report questionnaire were found to be at a high risk of psychosis (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Gooding, Tallent, & Matts, 2005). Some interviews, too, were designed to detect schizotypy, such as the Structured Interview for Schizotypy (Kendler, Lieberman, & Walsh, 1989) based on DSM schizotypy criteria. There is evidence that study methodology, sample characteristics (general population versus college students), use of questionnaires versus interview measures, and the item content of the measures used may influence estimates of schizotypy and its determinants (Cohen, Mohr, Ettinger, Chan, & Park, 2015; Tarbox & Pogue-Geile, 2011). The psychometric structure of schizotypy has been examined in several factor analyses of questionnaire data. The best replicated structure is a three-factor model including: the *cognitive perceptual dimension* (positive schizotypy), which includes hallucinatory and delusion-like experiences; the *disorganised dimension*, which refers to formal thought disorder and eccentric behaviour; and the *interpersonal dimension* (negative schizotypy), which concerns loss of emotional, physical, and social functions (Boyda, Shevlin, Mallett, Murphy, & Houston, 2013; Raine et al., 1994).

Whether and to what extent these dimensions of schizotypy are related to the risk of schizophrenia is still a matter of debate (Debbané & Barrantes-Vidal, 2015). A research

work has focused on the role of the neuropsychological mechanisms associated to schizotypy as possible mechanisms implicated in the development of the psychotic disorder (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014, 2015).

Schizotypy and cognition

Some studies found that individuals from the general population with schizotypal traits may show the same cognitive deficits as patients with schizophrenia, albeit with attenuated severity (Nelson, Seal, Pantelis, & Phillips, 2013; Yung & Nelson, 2013). These cognitive deficits can precede psychotic episodes and predict the onset of the illness in individuals at risk of schizophrenia (Nuechterlein, Ventura, Subotnik, & Bartzokis, 2014). A number of studies observed that some patients with schizophrenia had a history of pre-morbid intellectual deficits and learning difficulties since childhood and adolescence (Keefe, 2014), and low functioning throughout their lives; other people experienced functional decline due to prodromes, or in the early years of the illness following normal early development (Bora et al., 2014; Harvey, 2014).

Studies conducted in the general population and in student populations with schizotypy traits reported heterogeneous findings regarding this cognitive decline. High scores on schizotypy measures were associated with impairments in: verbal IQ (Noguchi, Hori, & Kunugi, 2008), working memory (Gooding & Tallent, 2003; Kerns & Becker, 2008; Koychev, El-Deredy, Haenschel, & Deakin, 2010; Matheson & Langdon, 2008; Park et al., 1995; Park & McTigue, 1997; Schmidt-Hansen & Honey, 2009; Tallent & Gooding, 1999), attention (Bedwell, Kamath, & Baksh, 2006; Bergida & Lenzenweger, 2006; Chen, Hsiao, & Lin, 1997; Gooding, Matts, & Rollmann, 2006), incidental learning (Burch, Hemsley, Corr, & Gwyer, 2006; Jones, Gray, & Hemsley, 1992), executive functions (Cappe, Herzog, Herzig, Brand, & Mohr, 2012; Gooding, Kwapil, & Tallent, 1999; Raine, Sheard, Reynolds, & Lencz, 1992), and verbal fluency (Cochrane, Petch, & Pickering, 2012). A recent meta-analysis (Chun, Minor, & Cohen, 2013) including 33 papers observed that in college students, the group with high schizotypy scores demonstrated small-effect deficits in working memory and set-shifting abilities compared to others. However, this meta-analysis did not perform a sensitivity analysis based on the quality of the included studies. Another review (Ettinger et al., 2015) showed that the individuals who had been psychometrically identified as having schizotypy, presented reduced performance in selective and sustained attention, in working memory and incidental learning compared to individuals with low levels of schizotypy. These deficits were also reported in groups with a high clinical risk of psychosis (Bora et al., 2014; Bora & Murray, 2014; Nuechterlein et al., 2014).

A different line of investigation studied the links between the three dimensions of schizotypy and cognitive deficits. Some studies found that the cognitive deficits appear to be associated with the positive (Mohanty et al., 2008; Schmidt-Hansen & Honey, 2009; Vollema & Postma, 2002), or with the negative (Rosa et al., 2000; Smyrnis et al., 2007), or still with the disorganised dimension (Kerns, 2006; Vollema & Postma, 2002). At least one paper (Cochrane et al., 2012) evaluated the cognitive functioning in people with schizotypy and in patients with schizophrenia. They conducted two studies: the first generated the observation that high negative schizotypy was associated with deficit in verbal fluency, and high levels of positive schizotypy tended to predict enhanced inhibition control; the second study reported a similar relationship between negative symptoms and verbal fluency in patients with schizophrenia. Albeit limited, there seems to be evidence pointing towards some continuity between the cognitive deficits that can be observed in people with schizotypy, and those that can be observed in patients diagnosed with schizophrenia.

Cognitive deficits could be involved in the transition to psychosis of the individuals with high schizotypy, and might grow in number, pervasiveness and severity along the schizophrenia spectrum. To the best of our knowledge, only one meta-analysis and two reviews have examined the neuropsychological correlates of schizotypy (Chun et al., 2013; Ettinger et al., 2014; Nelson et al., 2013).

This study aims to provide a more comprehensive understanding of cognitive impairments related to schizoytpy. We aimed at updating and expanding the results of past reviews, also taking into account the quality of the studies.

A systematic review was performed of all the studies assessing neuropsychological functions in individuals, who were assessed for schizotypy with validated scales or interviews. Thereafter, findings of case-control studies with complete data were meta-analysed by taking into account the following functions: global function, language, learning, attention, verbal and visual memory (short- and long-term), verbal and visual working memory, setshifting, processing speed, fluency, cognitive flexibility, and visual-spatial abilities. Studies were assessed for quality, while the sensitivity analysis was based on the quality and heterogeneity of the studies.

In order to identify similarities and differences between schizotypy and schizophrenia as far as the investigated cognitive domains were concerned, we compared the findings of this meta-analysis on schizotypy with the results observed in past meta-analyses of studies on patients with schizophrenia who had been assessed on the cognitive domains detailed in the measurement and treatment research to improve cognition in schizophrenia (MATRICS) consensus cognitive battery (MCCB, Green et al., 2004).

Method

Procedure

The preferred reporting items for systematic reviews and meta-analyses guidelines were used to conduct the meta-analysis (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). PubMed/MEDLINE and PsycINFO were searched from 1987 to 2014 using the key words "schizotypy AND cognition". Search details: "schizotypy" [All Fields] AND ("cognition" [MeSH Terms] OR "cognition" [All Fields]).

Two authors assessed all the retrieved articles for inclusion, on the basis of their titles and abstracts. A third author assessed independently the selected papers again and reviewed the inclusion criteria. The selection *flowchart* is shown in Figure 1. Two authors extracted the data, and disagreements were solved by discussion.

Studies were included when they met the following criteria: (a) psychometrically defined schizotypy group from a clinical or general population; (b) studies including standardised neuropsychological measures (mean and standard deviation, correlations and



Figure 1. Flowchart. The different phases of the systematic review and meta-analysis, the number of records identified in the literature searches, the number of identified studies and of the excluded ones.

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other test statistics); (c) studies published in peer-reviewed journals, and (d) in the English language. There is evidence that:

systematic reviews that are based on a search of English language literature that is accessible in the major bibliographic databases will often produce results that are close to those obtained from reviews based on more comprehensive searches that are free of language restrictions. (Egger, Juni, Bartlett, Holenstein, & Sterne, 2003)

Unpublished studies, or results included in working papers, theses, or conference proceedings—the so-called gray literature —were excluded since selection bias in unpublished literature searches was found to be higher than in published literature (Egger et al., 2003; Ferguson & Brannick, 2012).

Review papers and studies that did not clearly define the neuropsychological measures, or that did not consider schizotypy in the evaluation of cognitive deficits, or that included neurologic or drugs effect were excluded.

Sixty-seven papers were extracted from a total of 281 papers (188 from PubMed, 93 from PsycINFO) for the systematic review and qualitative analysis. Only case-control studies were included in the meta-analysis. Out of 51 case-control studies, 40 were included in the meta-analysis and sensitivity analysis. For 11 case-control studies we were unable to precisely define the sample size of cases or of the controls, or mean or standard deviation was not reported.

Further consideration was given to the following factors for the qualitative analysis: whether diagnostic criteria were specified, how the criteria supported the diagnosis, whether the psychometric properties of the tool used to assess the main outcome were reported, whether an a-priori power analysis was performed, whether dropouts were reported or not, and whether limitations were reported.

Neuropsychological measures

The articles were screened for the use of standardised neuropsychological assessment instruments, individual instruments (single cognitive test), or cognitive test using batteries of instruments. Neuropsychological measures examining different cognitive functions were analysed.

We evaluated the following domains: global cognition (e.g., Wechesler Adult Intelligence Scale WAIS, NART), language (e.g., vocabulary of WAIS), fluency (e.g., letter fluency from one minute per letter or category fluency), processing speed (e.g., Trail Making Test-A, WAISI DSST Coding), set-shifting (e.g., Trail Making test-B), visualspatial ability (e.g., Rey-Osterrieth Complex figure test), attention (e.g., Continuous Performance Test), verbal (e.g., Digit span) and visuo-spatial working memory (e.g., Dot Test), long verbal (California Verbal Learning Test CVLT, delayed recall) and visual memory (e.g., Rey-Osterrieth Complex figure test), short visual (e.g., Rey-Osterrieth Complex figure test, immediate recall) and verbal memory (e.g., California Verbal Learning Test CVLT, immediate recall), cognitive flexibility (e.g., Wisconsin Card Sorting Test; Stroop Color Word Test SCWT), and learning (e.g., CVLT, 3–5 trials). Categorisation was based on test manuals and on a previous meta-analysis (Chun et al., 2013). See Box 1 for details.

Domains	Definition	Neural areas involved
Global cognition or intellectual ability	Cognition comprising sensory, perceptual, associative and relational knowledge. It is the sum of cognitive processes including coding of information, planning and attention and arousal (Hilsenroth, Segal, & Hersen, 2003)	Left prefrontal—temporal-parietal network
Language	Ability to acquire and use complex communication system (Faust, 2012)	Angular Gyrus, Supramarginal Gyrus, Broca's area, Wernike's Area, Primary Auditory Cortex (Hart et al., 2007)
Learning	Acquisition of new information refers to the ability to store information. Learning implies consolidation (Lezak, Howieson, Loring, Hannay. & Fischer, 2004)	Hippocampus, amygdale and frontal lobe (Lezak et al., 2004)
Attention	The behavioural and cognitive process of selectively concentrating on one aspect of the environment while ignoring other things (Anderson, 2010)	Frontal-parietal network (Long, 2005)
Set-shifting	The ability to shift attention from one task to another (Kolb & Whishaw, 2006)	Anterior cingulate cortex and prefrontal cortex (Kolb & Whishaw, 2006)
Processing speed	Refers to the speed of cognitive processes and response output (Lezak et al., 2004)	Fronto-parietal network (Rypma et al., 2006) Parietal and temporal cortices and left middle frontal gyrus (Turken et al., 2008)
Short-term memory (STM)	The first stage of short-term memory (STM) storage temporarily holds verbal or visual information retained from the registration	Posterior temporal, parietal and prefrontal cortex (Kolb & Whishaw, 2006)—verbal STM. Parietal (intraparietal surcus) and occipital
 Immediate verbal memory Immediate visual memory 	minutes (Lezak et al., 2004)	2006), prefrontal cortex (Kolb & Whishaw, 2006)—visual STM
Long-term memory (LTM) • LT verbal memory • LT visual memory	The final stage of the dual memory in which data can be stored for long periods of time (Lezak et al., 2004)	Left frontal (Rösler, Heil, & Hennighausen, 1995), left temporal lobe and temporal neocortex (Kolb & Whishaw, 2006). Hippocampal and medial temporal lobe structure and neocortex—verbal LTM (Lezak et al., 2004)
		Parietal, occipital and right temporal areas (Kolb & Whishaw, 2006; Rösler et al., 1995)— visual LTM
Working memory (WM)	The ability to provide temporary active maintenance of information and enable manipulation and processing of information. It is	Left fronto-temporal cortex—working verbal memory (Thomason et al., 2009) Prefrontal and post parietal cortex—visual
 Verbal working memory Visual spatial working memory 	involved in retrieving data from long-term memory (Baddeley, 1992). It consists in two subsystems: one processing language-phonological loop—	working memory (Curtis, 2006; Zimmer, 2008)
	Verbal WM; - the other, visuo-spatial data—Visuo-spatial working memory	
Verbal Fluency	Ability to organise output in terms of clusters of meaningfully related words (Lezak et al., 2004)	Frontal lobe, left dorsolateral prefrontal cortex; left dorsolateral prefrontal cortex; left inferior
 Phonemic Semantic		nontal gylus (Alvalez & Enlory, 2000)
Cognitive flexibility	Mental ability to switch between thinking about two different concepts, and to think about multiple concepts simultaneously (Scott, 1962)	Anterior cingulate cortex (Peterson et al., 1999) and prefrontal cortex (Harrison et al., 2005), basal ganglia, anterior cingulate cortex (ACC), and posterior parietal cortex (Leber, Turk-Browne, & Chun. 2008)
Visual spatial ability	Spatial visualisation ability or visual-spatial ability is the ability to mentally manipulate 2- dimensional and 3-dimensional figures	Network of fronto-parietal cortex (Watson & Chatterjee, 2012)

Box 1. Neuropsychological domains and neural areas involved.

Schizotypy measures

In the samples, schizotypy was established by means of a wide range of measures. Some studies used the *Structured Interview for DSM-III and IV Personality Disorder* for axis II disorders (First et al., 1995; Stangl, Pfohl, Zimmerman, Bowers, & Corenthal, 1985) and the Structured Interview for Schizotypy (Kendler et al., 1989). Most studies used self-report assessment of schizotypy: The *Schizotypal Personality Questionnaire* (SPQ); (Raine, 1991) and its short version, the 22-item SPQ-B (Raine & Benishay, 1995). Other self-report tools used in the reviewed studies were: *Chapman psychosis-proneness scales* (CPPS) including the *Perceptual Aberration Scale* (Chapman, 1978), *Magical Ideation Scale* (Eckblad & Chapman, 1983), *SocialAnhedonia Scale* and the *Physical anhedonia* (PhA) (Chapman, Chapman, & Raulin, 1976); different versions of the *Oxford-Liverpool Inventory of Feelings and experiences* (O-life) *scales* (e.g., 105 items, 43 items and 15 items) (Mason, 1995; Mason & Claridge, 2006); the *Schizotypal Personality Scale* (Claridge & Broks, 1984). See Box 2 for details.

In the majority of the studies included in this review, the sample was composed by students and was split into High and Low schizotypy often using the median value or the top percentile. Few studies were carried out on clinical samples and used the Structured clinical interview for DSM-IV (SCID) to make a diagnosis.

Meta-analysis procedure

All papers with mean and standard deviation for the neuropsychological measures and a case-control design were included in the meta-analysis. Effect size was calculated as Hedges' adjusted g with 95% confidence interval. Different tasks were used to assess each neuropsychological area taken into examination, and sometimes the scores of the

Box 2. General description of the most widely adopted measures used to define schizotypy in the included studies.

Outcome measure	Description
SCID-II (Structured Clinical Interview for DSM-IV Personality Disorder) (Stangl et al., 1985)	A semi-structured interview for personality disorders
SIS—The Structured Interview for Schizotypy (Kendler et al., 1989)	A semi-structured interview for assessing 20 schizotypal symptoms and 11 schizotypal signs
SPQ—Schizotypal Personality Questionnaire (Raine, 1991)	Seventy-four-item self-report assessment on T/F format- Range: 0–74 Threshold for schizotypy: 90-degree percentile distribution of collected scores
SPQ-B-Schizotypal Personality Questionnaire Brief (Raine & Benishay, 1995)	Twenty-two-item selfcreport assessment on Yes/no Range: 0–22 Threshold for schizotypy: 17
PAS-Perceptual Aberration Scale (Chapman, 1978)	Thirty-five-item self-report on T/F format Threshold for schizotypy: 19
MIS-Magical Ideation Scale (Eckblad & Chapman, 1983)	Thirty-item self-report on T/F Threshold for schizotypy: 21
SAS-Social Anhedonia Scale (Chapman et al., 1976)	Forty-eight-item self-report on T/F
PhA-Physical Anhedonia Scale (Chapman et al., 1976)	Sixty-one-item self-report on T/F Threshold for schizotypy (Males): 28 Threshold for schizotypy (Females): 20
O-LIFE—Oxford-Liverpool Inventory of Feeling and Experiences (Mason, 1995; Mason & Claridge, 2006)	One hundred and four-item self-report on yes/no
STA-Schizotypal Personality Scale (Claridge & Broks, 1984)	Thirty-seven-item self-report on yes/no

tasks went opposite directions: for example, high reaction time to complete the *trail* making task represents poor performance (negative direction), whereas a high number of words in the *fluency task* represents good performance (positive direction). To favour the best interpretation of the results, effect size (i.e., Hedges' g) was calculated in order to produce a positive effect size when the results favoured the schizotypy group (to the right of the forest plots in the Appendix), and a negative effect size when the results were unfavourable for the schizotypy group (to the left of the forest plots in the Appendix). Essentially, worse performances by people with schizotypy or schizotypal traits compared to the controls resulted in negative Hedges' g, better performances by people with schizotypy or schizotypal traits compared to the controls resulted in positive Hedges' g. The calculated Hedges' g and its variance were analysed with the "metafor" package (Viechtbauer, 2010) and the "meta" package (Schwarzer, 2014) running in R version 3.0.2.(R Core team, 2013). The results of both the fixed-effects and random-effects models were reported. In the random-effects model, we estimated heterogeneity among studies using the empirical Bayes estimator (Morris, 1983).

Heterogeneity was assessed with Cochran's Q and I^2 statistics. Significant Q statistics (i.e., P < .05) was interpreted as suggestive of heterogeneity. For I^2 , values ranging 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; 75–100% represent considerable heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Funnel plot was also inspected for evidence of asymmetry and as a proxy index of bias in publication, as per Egger (Egger, Davey Smith, Schneider, & Minder, 1997).

Additional examination of heterogeneity in the meta-analysis was conducted with the Baujat plot (Baujat, Mahé, Pignon, & Hill, 2002), which shows the contribution of each study to the overall heterogeneity statistics on the *x*-axis, whereas on the *y*-axis it shows the influence of each study on the overall treatment effect, calculated as the standardised difference of the overall treatment effect with and without each study.

To control the adequacy of the models and outliers detection, both the radial plot (Galbraith, 1988, 1994) and the standardised residuals plot (Viechtbauer & Cheung, 2010) were considered. When outliers or influential cases were identified, the random-effects model was recalculated without the outliers/influential cases.

Models were also compared on the basis of the Akaike information criterion (AIC) (Akaike, 1987) and the Bayesian information criteria (BIC) (Schwarz, 1978). Models with the lowest AIC and BIC should be selected. As a rule of thumb, when the difference (Δ i) exceeds 10, the model with the lowest AIC/BIC should be preferred (Burnham & Anderson, 2002).

Unrestricted maximum likelihood meta-regression was used to assess the impact of moderators on the effects calculated by the models. Sensitivity analyses were applied only to neuropsychological areas with 10 or more studies.

Comparison between schizotypy and schizophrenia on cognitive domains

In order to determine the differences in neuropsychological performance between the people with schizophrenia and those with schizotypy, we compared our meta-analysis results with the findings of a meta-analysis of 23 studies including 1106 patients with psychotic disorders (90% of them having schizophrenia disorders and the rest having

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schizophreniform or schizoaffective disorders) and 1385 controls (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014).

The neuropsychological domains identified by our meta-analysis were compared with the cognitive domains based on the MATRICS consensus cognitive battery (MCCB, Green et al., 2004) and which are included in the meta-analysis by (Fatouros-Bergman et al., 2014). The following domains were not included: global cognition, language, and visuo-spatial ability. Different neuropsychological domains were collapsed into the broader cognitive domains of the MATRICS where, for example, processing speed includes two domains, speed of processing and fluency.

In the MATRICS, the reasoning and problem-solving domain is measured by the maze test, which instead is not used in the studies included in our meta-analysis and in the other one. The schizophrenia meta-analysis includes the executive function domain to analyse reasoning and problem-solving functioning. The cognitive tests that it incorporates correspond to the tests included in our meta-analysis to measure cognitive flexibility (which was evaluated in most studies by the Wisconsin Card Sorting Test) and set-shifting (tested with the Trail making test-B).

In both meta-analyses, the effect size and confidence of interval of the random-effect model were reported.

Results

Overall, 67 studies were included in the systematic review according to the inclusion and exclusion criteria.

The main characteristics of the included studies are summarised in Table A.1 in the Appendix. The included studies were conducted principally in America (N = 38) and Europe (N = 17); a minority of them was from Asia (N = 8) and Oceania (N = 4).

Results of review

Subjects with schizotypy versus healthy controls

Twenty-eight papers out of 51 with case-control designs (54%) found differences between the high and low schizotypy groups, with worse performances in the high schizotypy group.

Most papers found differences on *cognitive flexibility*, which was frequently measured by the Wisconsin Card Sorting Test (Cappe et al., 2012; Dinn, Harris, Aycicegi, Greene, & Andover, 2002; Gooding, Tallent, & Hegyi, 2001; Kim, Oh, Hong, & Choi, 2011; Lenzenweger & Korfine, 1994; Park et al., 1995; Poreh, Ross, & Whitman, 1995; Suhr, 1997), *spatial and working memory* (Koychev et al., 2010; Lenzenweger & Gold, 2000; Mitropoulou et al., 2005; Park et al., 1995; Park & McTigue, 1997; Schmidt-Hansen & Honey, 2010; Solanki, Swami, Singh, & Gupta, 2012; Tallent & Gooding, 1999), and *verbal working memory* (Cohen, Iglesias, & Minor, 2009; Hori et al., 2014; Kerns & Becker, 2008; Solanki et al., 2012; Wang, Chan, Shi, Cui, & Deng, 2008).

A few studies explored and observed differences in *verbal memory and learning* (Burch et al., 2006; Mitropoulou et al., 2005), *visual memory* (Gooding & Braun, 2004), *language* (Rapp et al., 2010), *processing speed* (Hori et al., 2014), *verbal fluency* (Cochrane et al.,

2012), global cognition (Goodarzi, Wykes, & Hemsley, 2000), and attention (Gooding et al., 2006; Macaulay & Cohen, 2013).

Contrarily to these findings, in two papers people with schizotypy presented better performance in *global cognition* (Gooding & Tallent, 2003; Pflum, Gooding, & White, 2013), *verbal working memory* (Gooding & Tallent, 2003), and *verbal memory and learning* (Cohen et al., 2009).

Relationship among schizotypy domains and cognitive functions

Correlation analyses exploring the relationship between schizotypy domains and cognitive deficits confirmed that schizotypal traits are related to a lower performance in *working memory and global cognition* (i.e., Matheson & Langdon, 2008; Noguchi et al., 2008), *attention* (Nuechterlein et al., 2002), *language* (Rapp et al., 2010), and *processing speed* (Hori, Matsuo, Teraishi, & Sasayama, 2012).

Poor cognitive performance appears to be associated with positive and negative schizotypy traits in the same way. *Cognitive flexibility* and *attention* were associated with negative (Dinn et al., 2002; Mohanty et al., 2008; Smyrnis et al., 2007), positive (Gooding et al., 2006; Mohanty et al., 2008), and disorganised (Kerns, 2006; Vollema & Postma, 2002) schizotypy traits, but deficit in *verbal learning and memory* (Vollema & Postma, 2002) and in *verbal working memory* were found to be associated with positive schizotypy only (Schmidt-hansen & Honey, 2010).

Lower *global cognition* (Chan et al., 2011; Rosa et al., 2000), *verbal fluency* (Cochrane et al., 2012), *visual memory* (Gooding & Braun, 2004) were found associated with negative schizotypy traits only.

For details, see supplementary material in Table A.1—systematic review of 67 papers.

Results of meta-analysis

The meta-analysis was conducted on 40 independent case-control studies and it detailed results on 15 neuropsychological areas. Only three areas were represented by 10 or more independent samples (global cognition, set-shifting, and phonetic and semantic fluency). For all the other areas, the findings were based on independent samples with less than 10 independent studies (Table 1).

Fixed-effects models showed evidence that global cognition, language, learning, attention, long-term visual memory, verbal working memory, visual spatial working memory, and cognitive flexibility were worse in people with clinically diagnosed schizotypy, or among those with higher scores on measures of schizotypy, than in controls (Table 1 and Figure 2).

The random-effects model only showed people with schizotypy or schizotypal traits to perform poorer than the controls in verbal working memory, visual spatial working memory and in language, with marginally and non-statistically lower performances on global cognition (Figure 3).

The differences in verbal working memory had the largest effect size.

Heterogeneity was substantial in most comparisons, but tended to decrease in the random-effects model without outliers, which almost always proved to be the best model on the basis of AIC and BIC (Table 1).

			Schizotypy	Hedges'				р-		р-	2				
		K	N	g	95%	% Cl	Ζ	value	Q	value	1² (%)	959	% Cl	AIC	BIC
Global cognition	Fixed model	19	943	-0.13	-0.22	-0.03	-2.66	<.01						25.6	26.6
	Random model	19	943	-0.17	-0.36	0.03	-1.80	.09	44.5	<.01	69.8	37.6	87.8	22.5	24.3
	Random model without outliers	18	902	-0.09	-0.20	0.02	-1.76	.10	19.1	.32	11.0	0.0	62.6	2.7	4.5
	Random model without outliers,	9	442	-0.16	-0.32	0.01	-2.05	.056							
	poor quality														
	Random model without outliers, good quality	9	460	-0.04	-0.19	0.11	-0.51	.61							
	Fixed model in SCID-II samples	2	114	-0.39	-0.67	-0.12	-2.78	.005							
Language	Fixed model	5	201	-0.23	-0.43	-0.03	-2.21	.03						-0.7	-1.1
	Random model	5	201	-0.23	-0.44	-0.02	-2.98	.04	2.21	.70	0.0	0.0	83.8	1.3	0.5
	Fixed model in SCID-II samples	1	82	-0.28	-0.62	0.04	-1.71	.08							
Learning	Fixed model	4	201	-0.26	-0.46	-0.06	-2.50	.01						18.0	17.4
	Random model	4	201	-0.20	-1.01	0.61	-0.78	.49	21.1	<.01	82.8	49.9	98.7	8.9	7.7
	Random model without outliers	3	119	0.07	-0.48	0.63	0.58	.62	2.0	.37	0.0%	0.0	97.8	2.6	0.8
	Fixed model in SCID-II samples	1	82	-0.23	-0.74	0.28	0.88	.37							
Attention	Fixed model	9	573	-0.18	-0.31	-0.05	-2.63	<.01						14.1	14.3
	Random model	9	573	-0.23	-0.52	0.05	-1.88	.10	22.7	<.01	67.0	23.8	91.4	11.0	11.4
	Random model without outliers	8	523	-0.12	-0.33	0.08	-1.42	.20	9.5	.22	27.3	0.0	83.3	3.4	4.1
Short-term verbal memory	Fixed model	9	456	-0.01	-0.15	0.16	0.09	.93						13.0	13.2
·	Random model	9	456	0.0	-0.30	0.29	-0.03	.98	20.3	<.01	61.4	14.2	89.6	11.2	11.5
	Random model without outliers	8	376	0.11	-0.07	0.29	1.44	.19	5.9	.55	0.0	0.0	72.9	1.5	1.7
Short-term visual memory	Fixed model	3	86	-0.29	-0.61	0.03	-1.78	.07						1.6	0.7
,	Random model	3	86	-0.29	-0.92	0.34	-1.97	.19	1.6	.44	0.0	0.0	96.9	3.6	1.7
Long-term verbal memory	Fixed model	7	362	-0.02	-0.18	0.15	-0.21	.84						14.2	14.2
	Random model	7	362	0.03	-0.31	0.37	0.21	.84	20.0	<.01	62.3	21.1	91.6	8.9	8.8
	Random model without outliers	6	217	0.18	-0.01	0.37	2.41	.06	2.9	.71	0.0	0.0	73.8	0.8	0.4
	Fixed model in SCID-II samples	1	82	-0.63	-0.97	-0.30	-3.70	<.001							
Long-term visual memory	Fixed model	5	290	-0.33	-0.52	-0.14	-3.36	<.01						9.6	9.2
	Random model	5	290	-0.27	-0.75	0.21	-1.58	.19	13.3	<.01	66.3	13.9	95.8	7.7	6.9
	Random model without outliers	4	145	-0.12	-0.55	0.31	-0.90	.43	3.8	.28	21.3	0.0	94.6	3.9	2.7
	Fixed model in SCID-II samples	1	82	-0.77	-1.11	-0.43	-4.44	<.001							
Verbal working memory	Fixed model	6	253	-0.75	-0.95	-0.55	-7.45	<.01						8.8	8.6
5 /	Random model	6	253	-0.70	-1.13	-0.27	-4.18	<.01	12.0	.03	61.6	0.0	94.2	9.4	9.0
	Fixed model in SCID-II samples	1	82	-1.02	-1.37	-0.67	-5.75	<.001							

Table 1. Effect sizes in meta-analysis of studies on cognition and schizotypy.

Visual spatial working memory	Fixed model	6	291	-0.42	-0.60	-0.25	-4.74	<.01						6.7	6.5
,	Random model	6	291	-0.42	-0.79	-0.05	-2.92	.03	11.3	.04	58.4	0.0	93.5	7.6	7.2
	Random model without outliers	5	146	-0.32	-0.57	-0.08	-3.71	.02	3.3	.50	0.0	0.0	81.1	1.7	0.9
	Fixed model in SCID-II samples	2	101	-0.50	-0.79	-0.20	-3.29	.001							
Set-shifting	Fixed model	15	581	-0.12	-0.24	-0.01	-2.11	.03						39.1	39.8
	Random model	15	581	-0.03	-0.30	0.23	-0.28	.78	52.1	<.01	75.8	51.6	90.0	23.5	24.9
	Random model poor quality	8	270	-0.02	-0.40	0.37	-0.09	.93							
	Random model good quality	7	311	-0.05	-0.45	0.35	-0.27	.79							
	Fixed model in SCID-II samples	1	82	-0.70	-1.03	-0.36	-4.04	<.001							
Processing speed	Fixed model	8	246	-0.11	-0.28	0.07	-1.22	.22						7.8	7.9
5 1	Random model	8	246	-0.07	-0.33	0.20	-0.59	.57	12.5	.08	31.7	0.0	79.6	7.4	7.5
	Random model without outliers	7	101	0.07	-0.07	0.21	1.22	.27	1.7	.94	0.0	0.0	28.3	0.8	0.7
	Fixed model in SCID-II samples	1	82	-0.59	-0.92	-0.25	-3.44	.001							
Fluency	Fixed model	10	408	0.01	-0.15	0.17	0.08	.93						16.1	16.4
	Random model	10	408	-0.04	-0.39	0.31	-0.25	.81	22.3	<.001	71.4	21.9	92.5	17.0	17.6
	Random model without outliers	9	370	0.08	-0.08	0.25	1.14	.29	5.92	.66	0.0	0.0	68.8	1.8	2.3
Cognitive flexibility	Fixed model	15	522	-0.16	-0. 28	-0.04	-2.56	.01						19.5	20.2
	Random model	15	522	-0.19	-0.41	0.02	-1.93	.07	31.3	<.01	59.9	18.3	85.1	17.6	18.9
	Random model without outliers	14	500	-0.14	-0.33	0.05	-1.59	.14	23.1	.03	45.7	0.0	80.3	11.9	13.2
	Random model poor quality	7	189	-0.19	-0.49	0.10	-1.42	.18							
	Random model good quality	7	311	-0.10	-0.36	0.16	-0.82	.43							
Visual spatial ability	Fixed model	4	90	-0.28	-0.55	0.0	-1.95	.05						1.1	0.5
	Random model	4	90	-0.28	-0.62	0.07	-2.54	.08	1.8	.62	0.0	0.0	88.2	3.1	1.9



Figure 2. *Fixed-effect model estimates/all functions*. The fixed-effect model of all neuropsychological functions analysed in the meta-analysis.



Figure 3. *Random-effect model estimates/all functions*. The random-effect model of all neuropsychological functions analysed in the meta-analysis.

The studies based on samples of people with clinically diagnosed schizotypy showed the greatest differences between patients and controls, with people with clinically diagnosed of schizotypy performing worse than controls, although this finding depended on just one study in most areas (Table 1).

Details on the analysis of each single neuropsychological area can be found in the supplementary material (Forest plot and Diagram of single neuropsychological areas).

The qualitative analysis showed that 21 studies had the best quality (Table A.2, Appendix). The sensitivity analysis based on quality was applied to the best model for neuropsychological areas with 10 or more studies. The quality of the studies did not change the estimates of the best model significantly, and it was found not to impact on heterogeneity.

We were unable to provide a sensitivity analysis of the results by subtype of schizotypy measure or dimension, since too few studies were available by neuropsychological areas.

Comparison between schizotypy and schizophrenia

The results of the comparison of the two meta-analyses are detailed in Box 3.

Cognitive domains OF MATRICS	Neuropsychological domains		Schizotypy	Schizophrenia					
		Ν	Effect size (95% CI)	Ν	Effect size (95% CI)				
Processing speed	Processing speed	246	-0.07 (-0.33; 0.20)	361	-1.03 (-1.23; -0.82)***				
	Fluency	408	-0.04 (-0.39;0.31)						
Attention/vigilance	Attention	573	-0.23 (-0.52; 0.05)*	364	-0.80 (-0.95; -0.65)**				
Working memory	Verbal working memory	253	-0.70 (-1.13; -0.27)**	375	-0.97 (-1.25; -0.69)***				
	Visuo-spatial working memory	291	-0.42 (-0.79; -0.05)*						
Verbal memory	Learning	201	-0.20 (-1.01; 0.61)*	567	-1.03 (-1.44; -0.63)***				
	Short-term verbal memory	456	0.0 (-0.30; 0.29)						
	Long-term verbal memory	362	0.03 (-0.31; 0.37)						
Visual memory	Short-term visual memory	86	-0.29 (-0.61;0.03)*	326	-0.78 (-1.21;-0.34)**				
,	Long-term memory	290	-0.27 (-0.75; 0.21)*						
Executive functions	Cognitive flexibility	522	-0.19 (-0.41;0.02)	529	-0.74 (-0.85;-0.62)**				
	Set-shifting	581	-0.03 (-0.30;0.23)						

*Small effect size (0.20-0.50); **Medium effect size (0.51-0.80); ***Large effect size (>0.80).

When considering only the cognitive domains of MATRICS, the schizotypy group performs worse in working memory than controls. Conversely, the patients with schizophrenia reported a worse performance than controls in all cognitive domains, but differences in verbal memory, working memory and processing speed had larger effect size.

Discussion

This is the most comprehensive systematic review and meta-analysis of cognition in people diagnosed with schizotypy or with schizotypal traits, as detected by high scores on psychometrically valid schizotypy measures.

Findings of the systematic review

In the systematic review, we observed various negative neurocognitive areas related to schizotypy, principally: cognitive flexibility, verbal and visuo-spatial working memory. The levels of impairment in different cognitive domains have been related to specific schizotypy traits. Cognitive flexibility was associated with disorganised (e.g., Vollema & Postma, 2002) and negative (e.g., Dinn et al., 2002) traits. Deficit in verbal working memory was observed in positive traits (e.g., Schmidt-Hansen & Honey, 2009), but not in negative ones. Previous review observed that the high level of positive and negative traits was associated to working memory impairments (Ettinger et al., 2015).

Some studies reported that higher levels of schizotypy were associated with better performance in global cognition, verbal working memory (Gooding & Tallent, 2003), and memory (Cohen et al., 2009).

Findings of meta-analysis

The previous findings were partially confirmed in the meta-analysis. We found differences in the fixed-effects model, which did not generalise to the random-effects model. Fixed-effects models are only designed to make a conditional inference about the k studies

included in the meta-analysis, and they can provide perfectly valid inferences under heterogeneity as long as these inferences are restricted to the set of studies included in the metaanalysis (Viechtbauer & Cheung, 2010). According to these models, we found that global cognition, language, learning, attention, verbal and visual-spatial working memory, visual memory, and cognitive flexibility were worse in people with clinically diagnosed schizotypy, or among those with higher scores on measures of schizotypy, than controls.

The random-effects model provides inference about the average effect in the literature, the included studies are assumed to be a random selection of. Therefore, only findings from the random-effects model can be generalised. Heterogeneity was substantial in most comparisons, and many comparisons contained too few studies. Estimates from the random-effects models should be considered with caution. Taking into account these caveats, we found evidence that people with schizotypy or with schizotypal traits present the worst functioning in working memory (both verbal and visual-spatial working memory), language, and have a marginally statistically significant poorer performance in global cognition compared to their controls.

The cognitive flexibility impairment effect—previously observed in the systematic review—disappears in the meta-analysis; only the deficit of verbal and visual-spatial working memory remains. Meanwhile, language and global cognition emerge from the meta-analysis only.

This result suggested that the working-memory deficit—the ability to store and manipulate information—could be a cardinal feature of the schizotypy personality disorder, and of the risk of psychosis. In line with our findings, previous studies (McClure et al., 2007; Zouraraki et al., 2016) observed that students with schizotypy presented working memory deficits. Additionally, previous reviews (Chun et al., 2013; Ettinger et al., 2014, 2015) observed similar findings but they did not distinguish verbal from visuo-spatial working memory. This meta-analysis highlights that verbal and visual processing abnormality underlies the working memory deficit in individuals diagnosed with schizotypy, and in individuals psychometrically identified as being affected by schizotypy.

Our meta-analysis reviewed also some papers that explored language production; we observed that individuals with high schizotypy showed difficulty in producing vocabulary.

Language abnormalities in schizotypy had been documented before. Kiang (2010) proposed that higher schizotypy is associated with speech containing idiosyncratic word usage and illogical associations. Another review (Ettinger et al., 2015) suggested that individuals with high schizotypy reported differences in the correct production and interpretation of non-literal language as metaphor, irony and proverbs similarly to patients with schizophrenia. Language comprehension in schizotypy could depend on semantic processing deficit (Tonelli, 2014). These anomalies may originate from decreased left lateralisation of language processing, or from working memory deficits caused by prefrontal dysfunction (Kiang, 2010). These abnormalities should not be surprising given that thought disorder is a defining feature of schizotypy (Coleman, Levy, Lenzenweger, & Holzman, 1996). Poor performance in language is also widely documented in patients with schizophrenia (Barrera, McKenna, & Berrios, 2005; Radanovic, Sousa, Valiengo, Gattaz, & Forlenza, 2013; Rodriguez-Ferrera, McCarthy, & McKenna, 2001; Yang et al., 2012) and might depend upon general intellectual ability impairments, and semantic deficits in particular. Language comprehension deficits may involve working memory deficits (Bagner, Melinder, & Barch, 2003; Caplan & Waters, 2013; Condray, Steinhauer, van Kammen, &

Kasparek, 1996). Clearly, both language and working memory deficits could influence social functioning (Yang et al., 2012).

We observed also global cognition impairment in the people with high schizotypy, though marginally statistically significant. Global cognition is usually assessed by a neuropsychological battery that comprises different cognitive functions, among which are: language subtest (e.g., vocabulary of the WAIS), working memory subtest (e.g., digits, and letters and numbers of the WAIS). The impairment found in global cognition could depend upon these domains.

In people with schizotypy other cognitive domains seem to be preserved, like attention, set-shifting, and cognitive flexibility. Contrarily, other studies observed deficits in attention (Ettinger et al., 2015), set-shifting (Chun et al., 2013) and executive performance in schizotypy groups (Zouraraki et al., 2016). The difference with our findings might be determined by the different neuropsychological measures used. Alternatively, it may depend upon the fact that people with high schizotypy traits do not meet the criteria of the schizotypy personality disorder; therefore, they do not manifest the same level of severity in cognitive dysfunction.

Similarities between schizotypy and schizophrenia on the MATRICS domains

The comparison between our meta-analysis with schizotypy groups and the other metaanalysis with patients with schizophrenia (Fatouros-Bergman et al., 2014) on the MATRICS domains highlighted that the working memory domain is the common impairment in both disorders.

Impairments in working memory have emerged as one of the cardinal features of schizophrenia (Forbes, Carrick, McIntosh, & Lawrie, 2009; McGrath, Chapple, & Wright, 2001), of affective psychotic disorders (Kristian Hill et al., 2015; McGrath et al., 2001), and in people at risk of psychosis (Bora et al., 2014).

Brain structural deficits could be underlying working memory deficit in schizotypy and schizophrenia (Corlett & Fletcher, 2012). One study observed that a high level of schizotypy was associated with a reduction of volume in the prefrontal cortex and temporal cortex (Raine et al., 1992), compatible with the reduction observed in schizophrenia. A fMRI study (Koenigsberg et al., 2005) showed that patients with schizotypy personality disorder manifested reduced activations in fronto-parietal areas when they were performing a visuo-spatial working memory task. Similar findings were observed in patients with first episode of psychosis (Broome et al., 2010) and in patients with schizophrenia (Manoach, 2003). Working memory deficit might represent a risk factor for the schizophrenia spectrum disorder. However the brain mechanism and cognitive dysfunctions underlying the common cognitive deficits in schizotypy and schizophrenia need to be investigated further.

This comparison based on the MATRICs domains could be very useful to understand the similarities between the two disorders, and to exclude some cognitive domains that might be deficient in schizotypy only.

Limitation

The major limitation of most studies on schizotypy is the reliance on self-report measures applied to student samples. The population of students might be biased on the risk of

schizophrenia, because outgoing psychosis has a detrimental effect on school performance so much so that many people with psychosis showed a decline in school performance during their childhood (Fuller et al., 2002; Keefe, 2014). As a consequence, samples with students are likely to include a very low fraction of participants showing a risk of schizophrenia, including those with schizotypy features.

Self-report measures have a limited ability to identify people with schizotypy, particularly when groups are created on the basis of median values in the sample. Quite obviously, someone may have high scores on a measure of schizotypy compared to his/her peers, and yet s/he may have scores well below the threshold that would qualify him/her as having schizotypy. This limitation was previously reported in another meta-analysis (Chun et al., 2013). Indeed the studies based on samples of people clinically diagnosed with schizotypy showed cases performing worse on many neuropsychological tests than controls to a wider extent than students' samples. Unfortunately, these studies are rare and their quality is not particularly high.

It is also important to ensure that measures are validated across different cultures. Culture can contribute to the expression of schizotypal traits (Cohen et al., 2015). The factor structure of schizotypy scales is generally preserved across cultures (Chan et al., 2015; Kwapil, Brown, Silvia, Myin-Germeys, & Barrantes-Vidal, 2012), but there is evidence that individual traits, particularly in negative schizotypy, vary as a function of culture. For example in the United States, Asian-Americans showed higher levels of negative schizotypy than Caucasians, whereas African-Americans showed the opposite (Cohen, Callaway, Najolia, Larsen, & Strauss, 2012). Another study (Sharpley & Peters, 1999) found that African-Caribbeans presented more delusional ideation compared to people in the UK. The studies reviewed in this meta-analysis contained an overrepresentation of samples from white, educated, industrialised, rich and democratic countries. This further limits the generalisability of the findings, well beyond heterogeneity in the studies. Besides these limitations, the results on some neuropsychological areas were produced by less than 10 studies, which prevents a firm conclusion on the findings. Nevertheless, results can be considered informative enough to be taken for clinical purposes in some specific areas, namely language, visuo-spatial, and verbal working memory.

Implication for research and clinical practice

These findings support the continuum between schizotpy and schizophrenia (Nelson et al., 2013). Schizotypy is an important topic to study the etiology of schizophrenia without the influence of antipsychotic medication or chronic hospitalisations. In addition, it is also relevant to investigate the association between schizotypy and mala-daptive behaviours—like drug use—that may increase the risk to develop psychotic disorders.

It is also important for the clinical practice. Early intervention targeting cognitive deficits may be crucial to the prevention of chronic disability, which should be a prominent target of therapy. The early identification of the affected cognitive factors allows focusing on the therapeutic targets to develop—namely reducing disability—rather than focusing on a later reduction of the more florid symptoms of the chronic illness (Gold, 2004).

Conclusion and future developments

Neuropsychological profile findings of schizotypy provide a standard of comparison for future studies evaluating the profile of cognitive impairments in other samples with schizotypy or related disorders. The findings on specific impaired domains may advance work on rehabilitation and prevention efforts. Future meta-analysis may review studies that compared cognitive functioning in people with schizotypy and schizophrenia, including social cognition, and examine the association with the different dimensions of schizotypy in-depth.

Future development may come from neuroimaging studies, which can be used to assess a broader range of neurofunctional mechanisms related to cognitive process.

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