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Is there a binding deficit in working memory in patients with schizophrenia? A meta-analysis

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ABSTRACT

In schizophrenia (SZ), a specific binding deficit in working memory (WM) has not yet been demonstrated, given that studies with various methodologies were conducted and the results obtained were heterogeneous. Thus, a meta-analysis of 10 WM studies was performed. Effect sizes were calculated for binding and control conditions. Analyses disclosed significantly lower scores in SZ patients relative to controls for both binding and control conditions. In addition, analyses revealed no greater impairments for the binding condition than for the control condition in SZ patients. Our meta-analysis suggests that there is no specific deficit of binding in WM in SZ.

1. Introduction

Working memory (WM) dysfunctions are a core feature of schizophrenia (SZ) (Silver et al., 2003). However, they are not homogeneous, as some authors have suggested that patients with SZ have more difficulties memorizing the association between information than the information itself (Burglen et al., 2004; Leiderman and Strejilevich, 2004; Salame et al., 2006; Altamura et al., 2013). This associative process is referred to as binding memory. The extent of the binding deficit in WM remains a contentious issue. For instance, some studies revealed a greater deficit in SZ patients for the binding condition than the control condition (Burglen et al., 2004; Leiderman and Strejilevich, 2004; Salame et al., 2006; Altamura et al., 2013; Gold et al., 2004), while others reported that both conditions were equally perturbed (Gold et al., 2003; Luck et al., 2010; Chhabra et al., 2013). However, all these studies were conducted with heterogeneous stimuli, different materials and parameters, limiting the establishment of a global principle. Thus, we performed a meta-analysis to establish whether there is a specific deficit of binding in WM in SZ. We also examined the impact of methodological factors that may contribute to heterogeneity of the results.

2. Methods

2.1. Literature search

A search was conducted in computerized databases – PubMed, Medline, PsycInfo and Embase – with the following keywords: "schizophrenia + working memory + binding" and "schizophrenia + working memory + association". Some studies were identified through the reference lists of reviews and previously-listed articles.

2.2. Inclusion criteria

The following inclusion criteria were considered in this meta-analysis: (1) Comparison between WM performance in adult patients with SZ and healthy controls; (2) diagnosis of SZ based on DSM IV criteria; (3) Inclusion of a binding condition, (i.e. in which participants had to memorize and recognize at least two bound information), and a control condition (i.e. in which participants had to memorize and recognize isolated information); (4) Reported information sufficient for effect size calculation. One study met the three first criteria, but did not report enough information for effect size calculation. We contacted first authors to request their results. Studies with non-parametric results were excluded.

2.3. Data analysis

The study data were analyzed by Comprehensive Meta-analysis software (Borenstein et al., 2005). Cohen's d was calculated to compute

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overall effect sizes for the binding and control conditions, separately, $d = (\mu_1 - \mu_2) / sd$ (μ: means, sd: standard deviation). We used preferentially discrimination scores (d′ or Pr index), or hit rates, accuracy means and t-values to estimate Cohen's d. Positive effect sizes reflect better performance in controls relative to patients. Conventionally, Cohen's d of 0.2, 0.5 and 0.8 is considered as being small, moderate and large, respectively (Cohen, 1988).

The significance of between-study heterogeneity was calculated with Q statistic. The magnitude of heterogeneity was estimated with the I^2 index: I^2 measures the proportion of inconsistency between studies' results attributable to heterogeneity (Higgins et al., 2003). Between-condition heterogeneity was also assessed with Q statistic to compare binding and control conditions. A significant Q statistic reflects an overall effect size significantly different between the two conditions. Given the heterogeneity in our dataset (see below), effect size estimates across studies were aggregated, in a random-effects model rather than a fixed-effect model, as it took into account between-study variability and therefore provided a more conservative estimate of composite effect size (Cooper et al., 2009).

To confirm whether methodological variables, such as stimuli modalities, task parameters or socio-demographic factors in the selected studies, may explain discrepancies in the literature, subgroup comparisons and meta-regression analysis were conducted as follows:

- Some studies found that patients with SZ performed significantly less for spatial than for verbal stimuli (Tek et al., 2002; Luck et al., 2008). Thus, subgroup comparisons were made between verbal and non-verbal tasks and spatial and non-spatial tasks;
- Binding in WM depends on memory load, with lower performance in patients for higher loads (Gold et al., 2003). Similarly, patients exhibited diminished performance for longer delays between encoding and retrieval (Dreher et al., 2001; Stephane and Pellizzer, 2007);
- Intelligence quotient (IQ) is closely linked to WM performance (Johnson et al., 2013), and it is known to be significantly lower in patients with SZ than in healthy controls (Woodberry et al., 2008; Hedman et al., 2013);
- Antipsychotic dose can differentially affect WM performance. Atypical antipsychotics are considered to improve cognition in patients with SZ (Keefe et al., 1999; Weickert and Goldberg, 2005), while typical antipsychotics do not (Bilder et al., 2002);
- Gender may influence WM performance in patients with SZ (Lecardeur et al., 2010);

A Bonferroni adjustment was performed to reduce false positives, with $\alpha = 0.005$.

Finally, publication bias enabled evaluation of the tendency to report only positive results. It was assessed with Egger intercept regression and fail-safe number. The fail-safe number identified the number of studies with nil effect size that could render p-values superior to alpha ($\alpha = 0.05$) (Egger et al., 1997).

3. Results

3.1. Overall analysis

The literature search, until September 2013, identified 301 articles, and 10 non-overlapping studies met our inclusion criteria (Fig. S1), with a total of 301 patients with SZ and 237 healthy controls. The characteristics of each study are described in Table S1.

Overall mean effect size was $d = 1.07$ for the binding condition (Fig. 1), and $d = 0.82$ for the control condition (Fig. 2). Analyses showed significantly lower performance for both conditions in patients with SZ relative to the controls ($p < 0.001$).

Between-study heterogeneity reached significance for the binding ($Q = 37.73$; $p < 0.001$; $I^2 = 76.14\%$) and control condition ($Q = 41.41$; $p < 0.001$; $I^2 = 78.28\%$). Between-condition heterogeneity was not significant ($Q = 1.49$; $p = 0.22$), with a low level of heterogeneity ($I^2 = 33.1\%$).

There was no publication bias for both conditions. Egger's regression did not reach significance for the binding ($p = 0.26$) and control conditions ($p = 0.92$). For the binding condition, the fail-safe number was 416, which means that 416 studies with no significant difference between patients with SZ and healthy controls were needed to reject the present significant result.

3.2. Moderators

Subgroup comparisons did not reach significance when examining stimuli modalities. Effect size was $d = 0.87$ [0.49 to 1.26] for verbal stimuli, $d = 1.18$ [0.72 to 1.84] for non-verbal stimuli, and between-subgroup heterogeneity was $Q = 0.45$; $p = 0.5$. Effect size was $d = 1.07$ [0.6 to 1.55] for spatial stimuli, and $d = 1.02$ [0.66 to 1.56] for non-spatial stimuli.

For the binding condition, correlations between effect sizes and clinical variables (age, education level, male/female ratio, IQ, atypical antipsychotic medication ratio, medication dose in chlorpromazine equivalent, delay, memory load and duration of stimulus presentation) were not significant (all $p > 0.005$) (Table S2).

4. Discussion

This meta-analysis revealed overall lower performance in patients with SZ than in healthy controls, with no greater deficits for bound information than for discrete information. Our results suggest that there is no specific binding deficit in WM in SZ.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chhabra 2012	0,673	0,222	0,049	0,238	1,108	3,033	0,002
Altamura 2012	1,188	0,222	0,049	0,753	1,622	5,357	0,000
Luck 2010	0,190	0,344	0,118	-0,484	0,864	0,553	0,580
Luck 2009	0,867	0,331	0,109	0,219	1,515	2,621	0,009
Luck 2008	1,457	0,365	0,133	0,742	2,173	3,993	0,000
Salame 2006	0,599	0,152	0,023	0,301	0,898	3,939	0,000
Burglen 2004	0,901	0,297	0,088	0,319	1,482	3,034	0,002
Leiderman 2004	2,313	0,340	0,116	1,647	2,979	6,802	0,000
Gold 2004	1,454	0,211	0,044	1,041	1,867	6,896	0,000
Dreher 2001	1,309	0,312	0,098	0,697	1,921	4,190	0,000
	1,077	0,169	0,029	0,746	1,408	6,377	0,000

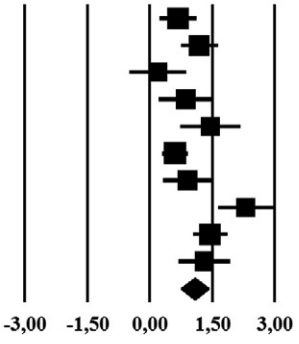

Fig. 1. Meta-analysis of the binding condition in WM tasks. Positive values reflect lower performance in SZ patients relative to healthy controls. CI: Confidence interval.