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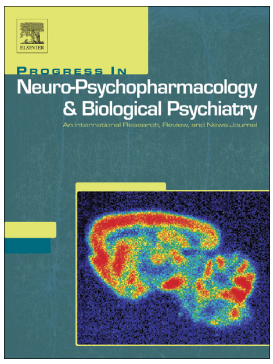

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Assessment of cognitive domains in major depressive disorders using the Cambridge Neuropsychological Test Automated Battery (CANTAB): systematic review and meta-analysis of cross-sectional and longitudinal studies.

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Abstract

Cognitive difficulties are known to persist after remission of symptoms and to affect psychosocial functioning and quality of life. Cognitive function, measured with the Cambridge Neuro-psychological Test Automated Battery (CANTAB), is a reliable approach to measure cognitive function in major depression. This systematic review and meta-analysis appraise cross-sectional and longitudinal studies that used specific CANTAB tests to measure cognitive function in major depression and the effect of treatment (PROSPERO ID: CRD42022355903). 1,212 studies were identified and 41 were included, 1,793 patients and 1,445 healthy controls. Deficits in executive functions were detected with the Stocking Of Cambridge (SOC) 'number of problems solved with minimal number of moves' and 'subsequent thinking time', Intra-Extra Dimensional Set Shift 'number of trials to complete the test', Spatial Working Memory 'strategy score' and 'between errors score', Spatial Span. Memory deficits were detected with Paired Associates Learning 'number of total errors', Pattern Recognition Memory (PRM) '% of correct answers' and 'response latency', Spatial Recognition Memory '% of correct answers', Delayed Matching To Sample (DMS) '% of total responses'. Impaired attention was detected by Rapid Visual Information Processing 'response latency' and probability to detect target'. Mental and motor responses increased when Reaction Time was measured. SOC 'number of problems solved with minimal number of moves', PRM 'response latency' and DMS '% of total responses' improved after a course of treatment. A range of variables including year of publication, age, IQ, severity and duration of illness influenced cognitive changes. The presence of significant cognitive deficits requires novel targeted interventions.

Key words: Major depressive disorders, depression, mood disorders, cognitive function, Cambridge Neuro- psychological Test Automated Battery, CANTAB, adults

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Introduction

There is evidence of cognitive dysfunction in mood disorders. In major (unipolar) depression approximately 60% of patients may be affected (1). Deficits are detectable in the presence of symptoms, can persist after remission (2) and constitute a risk factor for neurodegeneration (3). Considering that, major depression is a common condition with considerable morbidity (4) cognitive dysfunction is believed to be a significant contributor to disability and is an important treatment target to sustain full recovery.

Meta-analyses have demonstrated deficits in executive functions, memory, and attention (5–7) (8,9) in unmedicated patients (7), remitted patients (7,8), and in the presence of treatment refractoriness (8). So far, to our knowledge, there has not been a systematic appraisal of both cross-sectional and longitudinal literature to evaluate which cognitive domain is potentially amenable to modification following a course of treatment. This information could be an asset in establishing the effect of new treatments. In this work we expanded on previous meta-analyses by evaluating cross-sectional and longitudinal studies which assessed cognitive functions in major depression in comparison with healthy controls and before and after treatment.

Studies that used the Cambridge Neuro- psychological Test Automated Battery (CANTAB) were specifically selected for inclusion. This is because CANTAB is a validated battery of tests to assess multiple cognitive functions that allows a standardised evaluation of multidimensional neuropsychological functions. Using CANTAB to combine data from different studies offers the advantage of consistency and homogeneity over the variety of methods available. To our knowledge there has not been a meta-analysis in mood disorders which has evaluated individual

CANTAB tests to understand if confers additional accuracy and/or specificity in any given cognition domain.

Based on the available literature we expected that in comparison with healthy controls major depressive disorders overall would be characterised by cognitive deficits in executive functions, memory, and sustained attention. Furthermore, we predicted that neurocognitive tests assessing attention function would be more sensitive to change following treatment, based on the overall larger effect size of attentional deficits reported in the studies.

Methods

Literature Search

A comprehensive literature search was carried out by a medical librarian specialized in systematic searches (LÖ) and peer-reviewed by a subject specialist (DA) to include studies from the databases' inception up to July 2024, without language restrictions. Six biomedical databases were searched including PubMed, APA PsycInfo, Scopus, Web of Science, EMBASE, and Cochrane Library. PubMed and PubMed's MeSH were used to systematically identify search-term variations. A combination of the search-fields "title", "abstract" and "MeSH/Thesaurus" were applied for the best results. Key search terms included 'Depressive disorder', 'Major depressive disorder', 'CANTAB', 'Cambridge neuropsychological test automated battery' in addition to a range of antidepressants (see Supplementary information for a detailed description of the literature search). All records were uploaded to the systematic review software Covidence (Veritas Health Innovation, 2020, https://www.covidence.org) for automatic de-duplication, and blinded screening by two independent reviewers (TA and SJ). Selection discrepancies were

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resolved in the software by a third reviewer (DA). Identified work was extracted and cross-referenced (RR and DA). Selection and reporting of the literature was carried out in accordance with 'The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)' and the PRISMA-S extension and were informed by the Cochrane Handbook for Systematic Reviews of Interventions (10) (11). A PRISMA flow diagram was created to visually output the results of the search (12). PROSPERO ID for this systematic review and meta-analysis is CRD42022355903.

Inclusion criteria and quality assessment

The primary outcome measure was formal neurocognitive evaluation using specific neurocognitive CANTAB tests. Studies were selected if 1) investigated cognitive function with CANTAB in individuals experiencing a depressive episode in the context of unipolar disorders; 2) affected subjects were compared with healthy controls and/or 3) before and after specific treatment aiming at symptoms resolution; 4) The output of individual CANTAB tests could be combined as mean and standard deviation.

The effect of treatment was not included in the cross-sectional analyses as the cross-sectional analyses only compared measures of cognitive tests between cases and controls. Baseline data of longitudinal studies were considered whenever possible in the cross-sectional analyses. For these studies which also evaluated the longitudinal effect of an intervention in patients with depression, measures of cognitive functions of cases were imputed at baseline, before the treatment of interest commenced. In the longitudinal analyses, cognitive functions were measured before and after treatment in cases only.

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Two independent assessors screened and reviewed all the articles captured by the search (TA and SJ). A third author resolved conflicts by consensus (DA). Data extraction was carried out by a fourth author (RR) and reviewed by an independent reviewer (SJ) to ensure consistency. Quality assessment of the selected manuscripts was conducted by using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) (13) and the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses (14) by two authors operating independently from each other (RDG and SJ). Conflicts were resolved by a third author (DA).

Meta-analysis

A random effect meta-analysis was conducted with STATA 18.0 (Stata Corp, College Station, Texas) supplemented by 'Metan' software v4.02 (David Fisher, MRC Clinical Trials Unit at UCL, London, UK) as previously described (15,16). Studies were included if reported mean measurement of cognitive function which could be combined as mean and standard deviation (SD). Standardised mean differences were calculated using Cohen's *d* statistic. Random effects analyses were used throughout to weight each study (17). The effect of outliers was evaluated with the 'leave one out method' available in STATA. The presence of heterogeneity was tested using the *Q*-test with magnitude expressed with I^2 representing the proportion of effect size variance due to heterogeneity, where I^2 values of 0.25, 0.50 and 0.75 are respectively considered low, moderate and high (18) (10). When >3 studies were available, statistically significant heterogeneity was explored with meta-regressions for the largest dataset available for any given CANTAB test. Potential confounders considered included year of publication, age, sex (number of women), number of depressive episodes, length of illness, medication status, severity of depression and IQ. Egger's test was used to examine small study bias, alias the tendency of small

studies to report large effect sizes (e.g. publication bias) with a significance level set at $p \leq 0.05$ (19).

Results

A total of 1,212 studies were identified by the searches, 41 were included (24 cross sectional and 17 longitudinal), see Table 1 for details (20–55). This resulted in 1,793 patients (mean age 40.6 years, 64% women) and 1445 healthy controls. Longitudinal studies which included a sample of healthy controls at baseline were also included in the cross-sectional analysis. The study by Lazowski and colleagues combined results for unipolar and bipolar depression (56). The study by Sweeney and colleagues included patients with unipolar depression and bipolar disorders. Only patients with unipolar depression were included (24).

Quality assessment of randomised controlled trials suggested some risk of bias for all the studies except Kaser and colleagues considered at low risk (50). The highest risk of bias was for Lazowsky and colleagues (56). The Newcastle-Ottawa scale suggested a score ranging between 7 and 9 for case-control studies, with an average score of 8.24. Longitudinal studies scored between moderate to low quality. Details of the analyses are given below and summarised in Table 2 and Figures 2 and 3.

1) Executive functions

-Stocking of Cambridge (SOC): *computerised versions of the Tower of London to measure planning abilities.*

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a) The *number of problems solved with a minimal number of moves* was significantly less in major depression compared with healthy controls (N=13, 1,429 participants; SMD: -1.23; CI: -1.83, -0.64)(21,23–25,30,32,36,38–40,54,55,57). The risk of small study bias was significant suggesting the possibility of small-study bias (p=0.015). The analysis was not driven by any of the studies according to the sensitivity analysis and was highly heterogeneous (I^2: 95.7% p<0.001). Meta-regressions suggested that the number of problems solved decreased with longer duration of illness (Coeff: -0.06; 95% CI: -0.10 to -0.025; p=0.006) and increased with higher IQ (Coeff: 0.21; 95% CI: 0.04 to 0.38; p=0.022). Longitudinal studies suggested that the *number of problems solved with minimal moves* increased following treatment (N=7, 437 participants; SMD: 0.58; CI: 0.09, 1.07)(36,43,44,50,57–59). There was evidence of heterogeneity (I^2: 83.1% p<0.001) and no small studies bias (p=0.11).

b) *Initial thinking time* did not significantly differ in major depression in comparison with healthy controls (N=7, 574 participants; SMD: -0.03; CI: -0.46, 0.39)(23,27,30,32,36,39,57). There were no significant outliers. The analysis was free from small-study bias (p=0.34) and highly heterogeneous (I^2: 83.5% p<0.001). Heterogeneity was not explained by the variables considered in meta-regression (all ps>0.05). Longitudinal studies suggested no difference between baseline and endpoint (N=5, 349 participants; SMD: -0.62; CI: -1.57, 0.33) (36,43,57–59) in the presence of heterogeneity (I^2: 94.0% p<0.001) and no small-study bias (p=0.09).

c) *Subsequent thinking time* was increased in major depression in comparison with healthy controls (N=7, 574 participants; SMD: 1.40; CI: 0.62, 2.18)(23,27,30,32,36,39,57). There were no significant outliers. The analysis was free from publication bias (p=0.082) and highly heterogeneous (I^2: 93.8% p<0.001). Meta-regressions suggested that *subsequent thinking time* increased with severity of symptoms (Coeff: 7.69; 95% CI: 3.71 to 11.67; p=0.002) and

decreased with higher number of episodes (Coeff: -0.67; 95% CI: -0.97 to -0.37; p=0.002). Longitudinal studies suggested no difference between baseline and endpoint in subsequent *thinking time* (N=5, 347 participants; SMD: -0.87; CI: -2.30, 0.56) (36,43,57–59) in the presence of heterogeneity (I^2: 96.9% p<0.001) and no publication bias (p=0.28).

-Intra-extra dimensional set shift (IED): *cognitive flexibility.*

a) The *number of stages completed* was not different in major depression (N=11, 1385 participants; SMD: -0.21; CI: -0.68, -0.25)(20,23–25,30–33,37,40,55). The analysis was heterogeneous (I^2: 93% p<0.001) with no small studies bias (p=0.71). However sensitivity analysis suggested that the effect was driven by a subgroup of patients with significantly lower IQ (55). Once excluded, the *number of stages* was reduced in major depression (N=11, 1189 participants; SMD: -0.44; CI: -0.59, -0.29)(20,23–25,30–33,37,40,55). There was no evidence of significant heterogeneity (I^2: 23.3% p=0.20) or publication bias (p=0.86). There was not significant change following treatment in longitudinal studies (N=7, 381 participants; SMD: 0.14; CI: -0.06, 0.34)(33,41,43,44,53,57,58) in the absence of significant heterogeneity (I^2: 0.0% p=0.85) or publication bias (p=0.51).

b) The *number of trials to complete the test* was higher in patients with depression (N=6, 492 participants; SMD: 0.55; CI: 0.30, 0.81) (20,28,30,32,33,40). There were no outliers. There was no statistically significant heterogeneity (I^2: 36% p=0.14). There was no small-study bias (p=0.21). There were no longitudinal studies.

c) The *number of errors adjusted by the stages completed* did not differ in major depression (N=16, 1670 participants; SMD: 0.54; CI: 0.10, 0.98)(20,21,24,25,28,30–33,37,39–41,49,55,57). The analysis was heterogeneous (I^2: 93.2% p<0.001). There was no evidence of publication bias

(p=0.98) and no outliers. None of the variables considered explained the heterogeneity (all ps>0.05). Longitudinal data did not show a significant effect (N=6, 316 participants; SMD: -0.21; CI: -0.43, 0.01)(33,41,44,49,53,57) in the absence of significant heterogeneity (I^2: 0.0% p=0.44) and small-study bias (p=0.28).

d) The *number of intra-reversal trials* was not statistically significantly different between cases and controls (N=3, 330 participants; SMD: 0.78; CI: -0.13, 1.68)(24,28,39). There was evidence of significant heterogeneity (I^2: 93.1% p<0.001). There was no evidence of publication bias (p=0.25). There were no available longitudinal studies.

-Spatial working memory (SWM): *retention and recall working memory of spatial information.*

a) *Strategy score* indicates the ability to take advantage of predetermined strategies so that the lower the number of strategies the more efficient is the approach. The analysis suggested that in major depression the strategy score was increased vs. healthy controls (N=18, 1845 participants; SMD: 0.53; CI: 0.28, 0.78)(20–29,31,33,36,37,41,50,54–56). There was evidence of significant heterogeneity (I^2: 82.8% p<0.001) which was explained by the year of publication, in that the more recent the year of publication the larger the effect size (0.034; CI: 0.009; 0.059; p=0.01). There were no outliers. There was no evidence of publication bias (p=0.5). The strategy score was not affected in longitudinal studies (N=7, 527 participants; SMD: 0.13; CI: -0.25, 0.51)(33,36,41,43,50,56,58), there was evidence of heterogeneity (I^2:78.4% p<0.001) and no small studies bias (p=0.33).

b) *Between errors score* indicates errors in targeting the correct response. Patients with major depression made more errors compared with healthy controls (N=14, 1609 participants; SMD: 1.11; CI: 0.50, 1.71)(20,22,23,25,27–29,31,36,37,39,41,46,50,56). There was evidence of

significant heterogeneity (I^2: 96.2% p<0.001), no small studies bias (p=0.1) and no outliers. Heterogeneity was explained by age, with more errors made by younger patients (-0.11; CI: -0.21; -0.007; p=0.038), patients with less number of episodes (-1.38; CI: -2.51; -0.25; p=0.023) and lower IQ (-0.23; CI: -0.40; -0.06; p=0.018). There was no significant difference in *between errors score* in longitudinal studies (N=4, 292 participants; SMD: -0.02; CI: -0.39, 0.35)(36,41,50,56), heterogeneity was modest (I^2: 59.7% p=0.042), no small studies bias (p=0.49).

-Spatial span (SSP): *short-term memory of spatial information.*

Spatial span did not differ between depressed subjects and healthy controls (N=8, 583 participants; SMD: -0.27; CI: -0.60, 0.06)(21–25,28,31,60). There was significant heterogeneity (I^2: 71% p=0.001) and no small studies bias (p=0.18). The study by Grant and colleagues was however an outlier (25). Once removed, spatial span was reduced in major depression vs. healthy controls (N=7, 424 participants; SMD: -0.39; CI: -0.65, -0.13) with absence of significant heterogeneity (I^2: 39.9% p=0.12) and no publication bias (p=0.57). There were no longitudinal data available for analysis.

2) Memory function

-Paired associated learning (PAL): *visual memory and new learning.*

a) The number of *total errors (adjusted)* was higher in major depression vs. healthy controls (N=11, 864 participants; SMD: 0.36; CI: 0.1, 0.62) (24,25,30,32,36,40–42,49–51). There was evidence of significant heterogeneity (I^2: 68.8% p<0.001) no outliers or publication bias (p=0.2). Meta-regressions suggested that the *number of total errors* increased with duration of illness

(0.068; CI: 0.018; 0.11; p=0.019) and increasing age (0.02; CI: 0.03; 0.053; p=0.029). There was no significant difference when participants were re-tested in longitudinal studies (N=10, 572 participants; SMD: 0.46; CI: -0.98, 0.08)(34,36,41,43–45,49–51,58). There was evidence of heterogeneity (I^2: 88.5% p<0.001) and publication bias (p=0.028).

b) *First trial memory score* was not different between cases and controls (N=4, 287 participants; SMD: -0.30; CI: -0.77, 0.17)(36,41,50,51). There was evidence of heterogeneity (I^2: 73.2% p=0.005) which was not explained by the variable considered in meta-regression analyses (all ps>0.05). There was no evidence of outliers or small studies bias (p=0.59). For longitudinal studies there was a statistically significant increase between baseline and endpoint (N=6, 342 participants; SMD: 0.71; CI: 0.09, 1.34)(34,36,41,44,50,51). Heterogeneity was present (I^2: 86.2% p<0.001) and there was a trend towards statistically significant small study bias (p=0.051).

c) *Trials to success* was available for longitudinal studies and showed no significant difference for patients with major depression vs. healthy controls (N=5, 380 participants; SMD: -0.34; CI: -0.75, 0.07)(36,43,50,52,58). There was evidence of heterogeneity (I^2: 74.6% p=0.001) and no publication bias (p=0.12).

d) *Number of trials (adjusted)* was available for longitudinal studies and did not differ (N=6, 387 participants; SMD: -0.12; CI: -0.52, 0.28)(34,36,41,43,44,58). Heterogeneity was present (I^2: 72.5% p=0.001) with no publication bias (p=0.26).

-Pattern recognition memory (PRM): *visual working memory.*

a) *Percentage of correct answers* was decreased in major depression *(*N=11, 1291 participants; SMD: -0.63; CI: -1.24, -0.01)(20–25,27,28,31,46,47). There was evidence of significant

heterogeneity (I^2: 95.6% p<0.001) which was not explained by the available variables (all ps>0.05). There was no evidence of publication bias (p=0.28). Results from longitudinal studies indicated no significant effect (N=5, 260 participants; SMD: -0.08; CI: -0.36, 0.20)(34,43,45,52,58), in the absence of significant heterogeneity (I^2: 22.2% p=0.27) and strong evidence of small studies bias (p=0.008).

b) *Response latency* was increased in major depression vs. healthy controls (N=7, 842 participants; SMD: 0.42; CI: 0.04, 0.81)(20,22,23,27–29,46). There was evidence of significant heterogeneity (I^2: 82.3% p<0.001) which was not explained by the available variables (all ps>0.05). There was no evidence of small-study effect (p=0.58) and no outliers. Longitudinal studies suggested a reduction in *response latency* after treatment (N=3, 185 participants; SMD: -0.76; CI: -1.37, -0.14)(41,43,58), heterogeneity was significant (I^2: 75.1% p=0.018) with no evidence of small studies bias (p=0.21).

-Spatial recognition memory (SRM): *recognition memory for spatial locations.*

a) The *percentage of correct answers* was reduced in major depression compared to controls (N=11, 730 participants; SMD: -0.38; CI: -0.65, -0.11)(21–25,27,30,31,40,51,61). There was evidence of significant heterogeneity (I^2: 63.9% p=0.001) which was not explained by the variables considered (all ps>0.05). There was no evidence of statistically significant small-study bias (p=0.33). Longitudinal studies did not show a difference between cases and controls (N=6, 519 participants; SMD: -0.02; CI: -1.25, 1.20) (34,44,45,48,52,62). There was evidence of heterogeneity (I^2: 95.9% p<0.001) and no small-study bias (p=0.50).

b) *Response latency* was no different between cases and controls (N=5, 292 participants; SMD: 0.15; CI: -0.09, 0.38)(22,23,27,40,51). Heterogeneity was not significant (I^2: 0.0% p=0.72).

There was no evidence of publication bias (p=0.32). There were no longitudinal studies available.

-Delayed matching to sample (DMS): *visual matching and short-term recognition memory.*

a) The *percentage of total responses* was reduced in major depression vs. healthy controls *(*N=6, 409 participants; SMD: -0.57; CI: -0.84, -0.31)(23,27,28,38,54,61). Heterogeneity was not significant (I^2:38.8% p=0.14), there were no outliers and no evidence of publication bias (p=0.57). Longitudinal data showed that after treatment the percentage of total responses was higher *(*N=5, 251 participants; SMD: 1.00; CI: 0.74, 1.27)(34,43,45,58,61). There was no evidence of significant heterogeneity (I^2: 0.0% p=0.79) or publication bias (p=0.073).

b) *Responses to '0 sec. delay trials' matching to sample* were not different in major depression vs. controls *(*N=3, 307 participants; SMD: -0.32; CI: -0.88, 0.24)(21,24,25). Heterogeneity was significant (I^2:77.8% p=0.011). There was no evidence of publication bias (p=0.22). No longitudinal data was available.

c) *Responses to 'all delay trials' matching to sample* were not different in major depression vs. controls *(*N=5, 454 participants; SMD: 0.03; CI: -0.16, 0.23)(24,25,27,28,31). Heterogeneity was not significant (I^2: 0.0% p=0.76). There was no evidence of outliers or publication bias (p=0.18). Longitudinal data showed no difference before and after treatment *(*N=3, 235 participants; SMD: 0.36; CI: -0.08, 0.80)(33,43,58). There was no evidence of significant heterogeneity (I^2: 63.0% p=0.067) or publication bias (p=0.13).

3) Mental and motor response speed

-Reaction time (RTI): *mental and motor response speed.*

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Reaction time did not significantly differ in major depression in comparison with heathy controls (N=4, 373 participants; SMD: 0.22; CI: -0.09; 0.52)(25,29,37,49,56). There was no evidence of significant heterogeneity (I^2: 39.5% p=0.17) or publication bias (p=0.09). However, this result was driven by Grant and colleagues' study (25). By excluding this study reaction time was increased in major depression (N=3, 214 participants; SMD: 0.33; CI: 0.05; 0.62), with no heterogeneity (I^2: 0.0% p=0.42) or publication bias (p=0.15). Longitudinal studies did not show any significant difference before and after treatment either (N=4, 204 participants; SMD: -1.14; CI: -2.67; 0.40)(43,49,56,58). There was evidence of heterogeneity (I^2: 95.5% p<0.001) and no publication bias (p=0.16).

4) Attention

-Rapid Visual Information Processing (RVP): *sustained attention.*

a) *Response latency* was increased in major depression (N=10, 1101 participants; SMD: 0.99; CI: 0.25; 1.73)(20,28,29,36,38,41,46,50,51,55). There was no evidence of publication bias (p=0.15) but significant heterogeneity (I^2: 96.3% p<0.001) which meta-regressions suggested it was driven by IQ so that the lower the IQ the more pronounced the *latency* (-0.29; CI: -0.43; -0.15; p=0.004). The study by Yang and colleagues (55) which included a subgroup of subjects with lower IQ was an outlier and largely contributed to this effect. Once patients with lower IQ were excluded from the analysis, the effect was still present although the magnitude decreased (N=10, 905 participants; SMD: 0.42; CI: 0.20; 0.65). Longitudinal data suggested no significant effect (N=4, 286 participants; SMD: 0.31; CI: -0.03; 0.65)(36,41,50,51) with no heterogeneity (I^2: 50.8% p=0.087) and small-study bias (p=0.01). However, this result was driven by a subgroup of

patients in Herrera-Guzman's study, treated with a selective norepinephrine reuptake inhibitor (36). Once these patients were excluded treated patients showed a reduction in latency at endpoint (N=4, 212 participants; SMD: -0.42; CI: -0.83; -0.00) with no significant heterogeneity (I^2: 53.5% p=0.092) or publication bias (p=0.45).

b) *Probability to detect target* was reduced in major depression vs. healthy controls (N=4, 845 participants; SMD: -3.38; CI: -5.21; -1.54)(20,39,46,55). There was evidence of significant heterogeneity (I^2: 98.7% p<0.001) which was not explained by any of the variables considered (p>0.05) and there was evidence of publication bias (p=0.034), no outliers. No longitudinal studies were available.

c) *Correct score* was not different between cases and controls (N=4, 343 participants; SMD: -0.40; CI: -0.80; 0.01)(28,38,46,54). There was evidence of significant heterogeneity (I^2: 68.7% p=0.022) which was not explained by any of the variables considered (p>0.05) and there was no evidence of publication bias (p=0.51) or outliers. No longitudinal studies were available.

d) *Probability of false alarms* was not different between cases and controls (N=5, 854 participants; SMD: -0.07; CI: -0.78; 0.63)(38,39,46,54,55). There was evidence of significant heterogeneity (I^2: 94.8% p<0.001) which was not explained by any of the variables considered (p>0.05) and there were no outliers and no evidence of publication bias (p=0.39). There were no longitudinal studies available.

-***Match to sample visual search (MTS):*** *attention and visual searching.*

The *latency* in matching visual stimuli was not different in major depression vs. healthy controls *(*N=3, 389 participants; SMD: -0.09; CI: -1.03, 0.85)(25,27,54). Heterogeneity was significant (I^2: 94.6% p<0.001), which was not explained by the variables (all p values>0.05). There were

no outliers, and there was no evidence of publication bias (p=0.62). There were no longitudinal studies available.

Discussion

The aim of this work was to investigate studies of cognitive domains in major depression to understand 1) the contribution of specific CANTAB tests to cognitive function and 2) identify tests potentially sensitive to change following a course of treatment.

In summary, in relation to executive functions, deficits in planning abilities were detected by the Stocking of Cambridge (SOC) 'number of problems solved with minimal number of moves' and 'subsequent thinking time'. Reduced cognitive flexibility was evident with Intra-Extra Dimensional Set Shift (IED) 'number of trials to complete the test'. Spatial Working Memory (SWM) 'strategy score' and 'between errors score' showed deficits in the ability to retain and recall spatial working memory information. Short term memory of spatial information, tested with spatial span (SSP), was also abnormal. SOC 'number of problems solved with minimal number of moves' was sensitive to improvement following a course of treatment.

With regard to memory deficits, visual memory and new learning were impaired when measured with Paired Associates Learning (PAL) 'number of total errors' similar to working memory measured as Pattern Recognition Memory (PRM) '% of correct answers' and 'response latency'. Other memory deficits included a reduction in recognition memory for spatial locations expressed as Spatial recognition memory (SRM) '% of correct answers and a reduction in visual matching and short-term recognition memory capacity, expressed as Delayed Matching to

Sample (DMS) '% of total responses'. PRM 'response latency' and DMS '% of total responses', improved after a course of treatment.

Lastly impaired attention was supported by reductions in sustained attention expressed as Rapid Visual Information Processing (RVP) 'response latency' and 'probability to detect target'.

Reaction Time (RTI) was the only CANTAB test to measure mental and motor response and was increased in depression when the study by Grant and colleagues was excluded (25).

Figures 2 and 3 provide details of the effect size of CANTAB tests that detected deficits in cognitive domains in major depression for cross-sectional and longitudinal analyses. Figure 3 and Table 2 indicate that based on the available data, SOC 'problem solved', PRM 'response latency' and DMS 'total responses' are sensitive to detect response following a course of treatment.

Results confirm the presence of reduced cognitive function in major depression, largely consistent with previous similar work (5,7,8,63). The most recent meta-analysis by Rhee and colleagues demonstrated moderate cognitive deficits in the same domains in major depression with worse profiles in case of treatment resistance and advanced age and no effects in children. In agreement with these authors, we noted that advancing age and duration of illness tend to increase the effect size. In addition, higher IQ can be protective whilst severity of illness, more recent year of publication were associated with worse cognitive profiles. Differently to Rhee and colleagues we did not include treatment resistant depression as the information was not available in the primary studies and we excluded children because of the uncertainty regarding comparability of cognitive profile in children and the very small number of studies. Finally, Rhee and colleagues noted that reaction time was not increased in unipolar depression (8). Similarly to

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pioneering work by Rock and colleagues (7), we found that this effect is driven by an individual study (25). Results presented here expands on Rhree's and colleagues work by providing information on individual CANTAB tests and evidence of what tests might be susceptible to improvement following a course of treatment and by including a larger number of studies.

According to our analysis the largest deficit was in the visuospatial memory domain, followed by working memory and executive functions. To our knowledge, there are limited effective treatments available to improve cognitive function in major depression in these domains. Cognitive remediation has been shown to have a positive but modest effect on global cognition, verbal memory, attention/processing speed, working memory, and executive functioning although no significant improvements in visuospatial memory(64). Selective serotonin reuptake inhibitors (SSRIs) have been shown to modulate cognitive function in depression in a range of key cortical and subcortical areas (65,66), and to have the largest effects although still modest among antidepressants on attention, executive function, immediate memory, processing speed, recent memory and sustained attention (67). More recently the augmentation of the SSRI escitalopram with low dose aripiprazole (5mg/day) has been shown to enhance cognitive function in depression (68). New pharmacological treatments in major depression with the potential for cognitive remediation include multimodal antidepressants such as Vortioxetine (69), whereas the effect of novel treatments for depression such as ketamine are still under investigation (70). Future research might benefit from specifically testing cognitive function to better understand the relationship between pharmacological action of novel compounds and treatment response (65,66).

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Limitations of this work include a relatively small pool of studies available for analysis which is reflected in the detection of small-study bias in some of the analyses. For this reason, even in the absence of statistical significance, the occurrence of such bias cannot be entirely ruled out. The small-scale nature of the reports which were often non-controlled, experimental type of studies is possible to have introduced sampling bias. This is irrespective of the quality assessment of the studies which was generally favourable. The other limitation is the significant high level of heterogeneity which dominated the analyses (75–100%) according to the Cochrane handbook (https://handbook-5–1.cochrane.org/front_page.htm).

We investigated all the confounders that were consistently reported in the studies by using meta-regression analyses to explore heterogeneity.

Although some of this heterogeneity could be explained by the variables considered in meta-regression analyses, with obvious predictors of effect size including age, severity of illness, duration of illness, year of publication, IQ, a large amount of variability is likely to be related to variables that could not be examined as patients' details were not always documented. This suggests that additional confounders potentially affecting the process of causation could not be fully identified in the work (15,16,71,72). Furthermore, it was not possible to carry out sub-group analyses because either the number of comparisons was too small (CANTAB cognitive tests were analysed individually) and/or information was not sufficiently reported (e.g. first episode vs. recurrent depression).

It is important to mention that it was not possible to exclude patients with bipolar depression that were analysed together with unipolar depression in the study by Lazowski and colleagues (56).

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Although this could have introduced a bias, sensitivity analysis did not indicate that this study affected the results.

The analysis included healthy controls from cross-sectional and longitudinal studies. Even though cases and controls were matched, the aim of cross-sectional and longitudinal studies were different, the latter group aiming largely at treatment effects on cognition. Hence, it is possible that the difference might have introduced a bias, not least in the selection of the healthy controls recruited in the studies.

Finally, it is important to mention that although CANTAB tests a wide range of cognitive dimensions, some cognitive functions were not assessed (e.g. explicit memory, attentional process, etc).

In conclusion, this study provides a detailed appraisal of CANTAB tests that can be used to identify cognitive deficits in major depression and improvement after treatment. Affected domains include executive functions, memory, and sustained attention. The significance of these deficits and the documented impact on patients require the development of novel targeted treatment in adjunct to what is already available.

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Declaration of competing interests

AHY is employed by King's College London and is a Honorary Consultant psychiatrist at South London and Maudsley NHS Foundation Trust (NHS UK). He is Editor of Journal of Psychopharmacology and Deputy Editor of BJPsych Open. He has delivered paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Flow Neuroscience, Novartis, Roche, Janssen, Takeda, Noema pharma, Compass, Astrazenaca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, Sage, Neurocentrx. He is the Principal Investigator in the Restore-Life VNS registry study funded by LivaNova. He is also the Principal Investigator on ESKETINTRD3004 "An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression", "The Effects of Psilocybin on Cognitive Function in Healthy Participants", "The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)", "A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy'' (Janssen), "An Open-label, Long-term, Safety and Efficacy Study of Aticaprant as Adjunctive Therapy in Adult and Elderly Participants with Major Depressive Disorder (MDD)'' (Janssen), "A Randomized, Double-blind, Multicentre, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aticaprant 10 mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder (MDD) with Moderate-to-severe Anhedonia and Inadequate Response to Current Antidepressant Therapy'', "A Study of Disease Characteristics and Real-life Standard of Care Effectiveness in Patients with Major Depressive Disorder (MDD) With Anhedonia and Inadequate Response to Current

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Antidepressant Therapy Including an SSRI or SNR" (Janssen). He is the UK Chief Investigator for Compass COMP006 & COMP007 studies and for Novartis MDD study MIJ821A12201. His grant funding (past and present) include NIMH (USA), CIHR (Canada), NARSAD (USA), Stanley Medical Research Institute (USA), MRC (UK), Wellcome Trust (UK), Royal College of Physicians (Edin), BMA (UK), UBC-VGH Foundation (Canada), WEDC (Canada), CCS Depression Research Fund (Canada), MSFHR (Canada), NIHR (UK), Janssen (UK) EU Horizon 2020. No shareholdings in pharmaceutical companies. The other authors have no competing interests to declare.

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None

Author contribution

DA conceived the idea, run the analyses and wrote the first draft of the manuscript. LÖ was involved in the identification of the studies prior to selection. RR TA, SJ, RDG, DA participated in the process of selection and quality appraisal of the studies. RR reviewed the studies and extracted relevant information. AHY and ES provided senior leadership to complete the manuscript. All the authors contributed to and approved the final version of the manuscript.

Data availabilities

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Data associated with this paper will be available from DA upon reasonable request.

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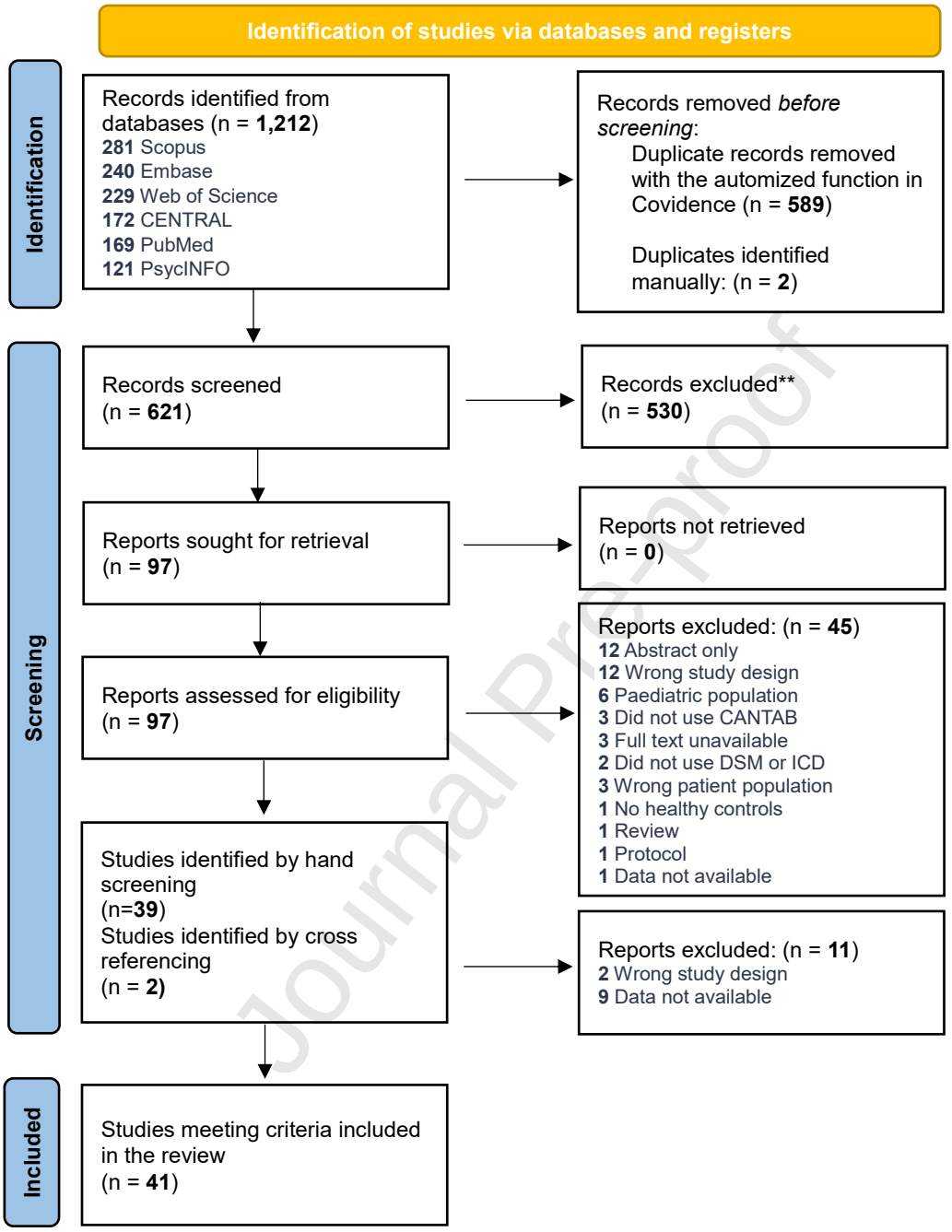

Figure 1: PRISMA flow diagram from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Authors	Year of Publication	N. Major Depression	N. Healthy Controls	Mean Age	N. Women	Medicated/Unmedicated	Diagnostic Criteria	Design	Intervention
Beats et al.	1996	24	15	72	12	21 medicated 3 unmedicated	DSM-III-R	CS	NA
Elliot et al.	1996	28	22	49.9	19	Medicated	DSM-III-R	CS	NA
Purcell et al	1997	20	20	37.5	12	12 medicated 8 unmedicated	DSM-IV	CS	NA
Sweeney et al.	2000	58	51	32.29	39	Medicated	DSM-IV	CS	NA
Grant et al.	2001	123	36	39	48	Unmedicated (for 28 days)	DSM-IV	CS	NA
Murphy	2003	27	23	38.9	14	Medicated	DSM-IV	CS	NA
Porter et al.	2003	44	44	32.9	29	Unmedicated (for 45 days)	DSM-IV	CS	NA
Weiland-Fiedler et al.	2004	28	23	37.8	18	Unmedicated	DSM-IV	CS	NA
Erickson et al.	2005	20	20	37.15	10	Unmedicated (for 21 days)	DSM-IV	CS	NA
Michopoulos et al. (Melancholic)	2006	11	11	50.9	11	Medicated	DSM-IV	CS	NA
Michopoulos et al. (Non-Melancholic)	2006	11	11	47.8	11	Medicated	DSM-IV	CS	NA
Taylor Tavares et al.	2007	22	25	38.6	17	Unmedicated	DSM-IV	CS	NA
Michopoulos et al.	2008	40	20	52.7	40	Medicated	DSM-IV	CS	NA
Reppermund et al.	2009	53	13	43.5	28	Medicated	DSM-IV	LNG	Mixed Antidepressants
Falconer et al.	2010	24	NA	52	17	Medicated	ICD-10	LNG	ECT
Heinznel et al.	2010	20	29	40	11	Unmedicated	DSM- IV	CS	NA
Herrera-Guzman et al. (SNRI)	2010	37	37	30.8	31	Medicated	DSM-IV	LNG	SNRI
Herrera-Guzman et al. (SSRI)	2010	36	37	30.8	31	Medicated	DSM-IV	LNG	SSRI
Lyche et al.	2010	37	91	44.2	23	13 medicated 24 unmedicated	DSM-IV	CS	NA
Maalouf et al.	2010	20	28	34.2	16	Medicated	DSM-IV	CS	NA
Braw et al. (<25 years)	2011	30	30	17.08	20	Unmedicated	DSM-IV	CS	NA
Braw et al. (25-45 years)	2011	30	30	35	16	Unmedicated	DSM-IV	CS	NA
Braw et al. (46-65 years)	2011	25	25	54	14	Unmedicated	DSM-IV	CS	NA
Tsaltas et al. (ECT)	2011	15	15	48.53	30	Medicated	DSM-IV-TR	CS	NA
Tsaltas et al. (Non-ECT)	2011	15	15	47.8	30	Medicated	DSM-IV-TR	CS	NA
Boeker et al.	2012	28	28	39.7	13	Medicated	DSM- IV	LNG	SSRI & MAOIs
Hermens et al.	2013	48	21	21.7	32	Medicated	DSM-IV-TR	CS	NA

Greer et al. (a)	2014	30	NA	31.7	19	Medicated	DSM- IV	LNG	Duloxetine
Ladegaard et al.	2014	44	44	32.5	33	Unmedicated	DSM-III-R	CS	NA
Lazowski et al.	2014	15	NA	46	9	Medicated	DSM-IV-TR	LNG	Olanzapine
Moreines et al.	2014	10	NA	42	10	Medicated	DSM-IV	LNG	DBS
Greer et al.	2015	39	NA	46.7	34	Medicated	DSM- IV	LNG	Exercise Augmentation
Kalogerakou et al.	2015	15	NA	48.67	15	Medicated	SCID	LNG	ECT
Maric et al.	2015	30	NA	47.3	17	Medicated	ICD-10	LNG	ECT
Yang et al.	2015	51	51	30.98	31	Unmedicated	DSM-IV	CS	NA
Liu et al.	2016	62	73	28.35	40	Unmedicated	DSM-IV	CS	NA
Sinclair et al.	2016	167	NA	56.85	64	Unmedicated	DSM- IV	LNG	ECT
Bergfeld et al.	2017	25	21	53.1	17	Unmedicated	DSM-IV	LNG	DBS & Optimisation
Kaser et al.	2017	30	30	43.97	19	Medicated	ICD-10	LNG	Modafinil
Salehinejad et al.	2017	12	12	26.8	7	Unmedicated	DSM- IV	LNG	tDCS
Stojanovic et al.	2017	29	NA	46.9	16	Medicated	DSM-IV & ICD-10	LNG	ECT
Han et al.	2020	18	22	31.22	10	Medicated	DSM- IV	LNG	Mixed treatments
Ozcan et al.	2020	30	NA	43.6	19	Medicated	DSM-IV	LNG	rTMS
Sanchez-Carro et al.	2021	74	68	49.73	52	Medicated	DSM-IV-TR	CS	NA
Yang et al. (IQ=100)	2021	100	165	27.13	61	Unmedicated	DSM-IV	CS	NA
Yang et al. (IQ=31)	2021	31	165	34	22	Unmedicated	DSM-IV	CS	NA
Luo et al.	2022	107	74	34.58	67	Medicated	DSM-5	CS	NA

Table 1: Details of the studies. CS: cross sectional study; LNG: Longitudinal study

Cognitive domain and CANTAB test	Cross-sectional	Longitudinal course	Change after treatment
Executive functions ***SOC: Planning abilities***			
-Number of problems solved	↓	↑	+
-Initial thinking time	↑↓	↑↓	-
-Subsequent thinking time	↑	↑↓	-
Executive functions ***IED: Cognitive flexibility***			
-Number of stages completed	↓	↑↓	-
-Number of trials to complete the test	↑	NA	-
-Number of errors adjusted by stages	↑↓	↑↓	-
-Number of intra-reversal trials	↑↓	NA	-
Executive functions ***SWM: Spatial working memory***			
-Strategy score	↑	↑↓	-
-Between errors score	↑	↑↓	-
Executive Functions ***SSP: Spatial short-term memory***			-
-Spatial span	↑↓	NA	-
Memory Function ***PAL: Visual memory and new learning***			
-Number of total errors (adjusted)	↑	↑↓	-
-First trial memory score	↑↓	↑	-
-Trials to success	NA	↑↓	-
-Number of trials (adjusted)	NA	↑↓	-
Memory Function ***PRM: Visual working memory***			
-Percentage correct answers	↓	↑↓	-
-Response latency	↑	↓	+
Memory Function ***SRM: Spatial recognition memory***			
-Percentage of correct answers	↓	↑↓	-
-Response latency	↑↓	NA	-
Memory Function ***DMS: Visual matching and memory***			
-Percentage of total responses	↓	↑	+
-Responses to 0 delay trials	↑↓	NA	-
-Responses to all delay trials	↑↓	↑↓	-
Mental and motor response speed ***RTI: Reaction time***			
-Reaction time	↑↓	↑↓	-
Attention ***RVP: Sustained attention***			
-Response latency	↑	↑↓	-
-Probability to detect target	↓	NA	-
-Correct score	↑↓	NA	-
-Probability of false alarms	↑↓	NA	-
Attention ***MTS: Attention and visual searching***			
-Latency	↑↓	NA	-

Table 2: Direction of change of CANTAB tests in major depression 1) in comparison with healthy controls (Cross-sectional) and 2) before and after treatment (Longitudinal) suggesting consistent change following treatment. CANTAB: Cambridge Neuro-psychological Test Automated Battery; SOC: Stocking of Cambridge; IED: Intra-Extra Dimensional Set Shift; SWM: Spatial Working Memory; SSP: Spatial Span; PAL: Paired Associates Learning; PRN: Pattern Recognition Memory; SRM: Spatial

recognition memory; DMS: Delayed Matching to Sample; RTI: Reaction time; RVP: Rapid Visual Information Processing; MTS: Match to sample visual search, NA: Not applicable.

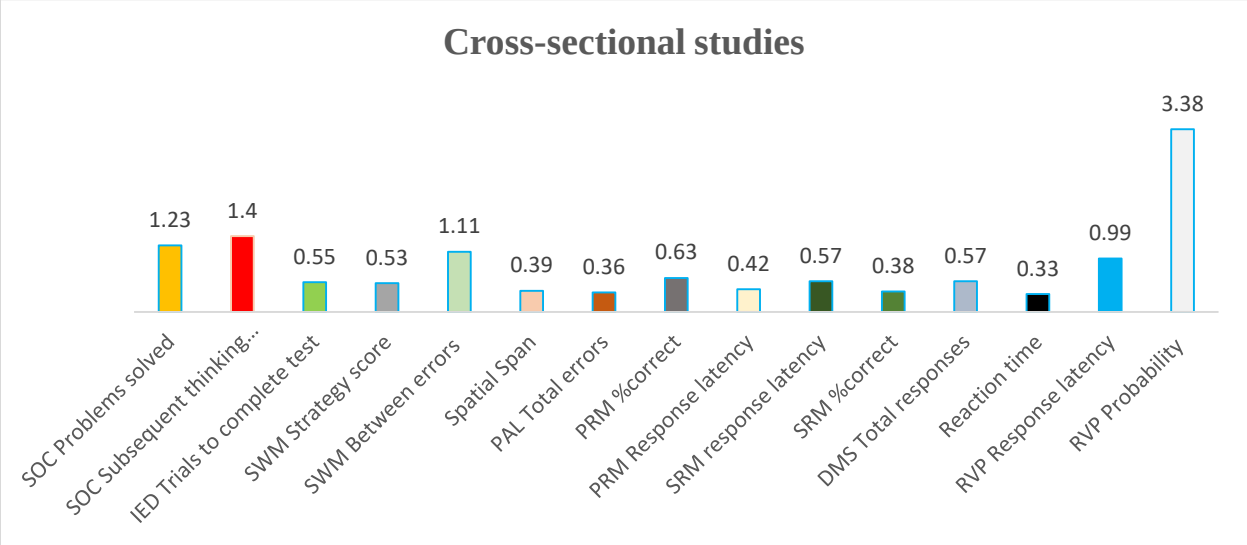

Figure 2: Comparison of the effect size (SMD) of CANTAB tests which show abnormalities in major depression vs. healthy controls (cross-sectional samples). CANTAB: Cambridge Neuro- psychological Test Automated Battery; SOC: Stocking of Cambridge; IED: Intra-Extra Dimensional Set Shift; SWM: Spatial Working Memory; PAL: Paired Associates Learning; PRN: Pattern Recognition Memory; SRM: Spatial recognition memory; DMS: Delayed Matching to Sample; RVP: Rapid Visual Information Processing.

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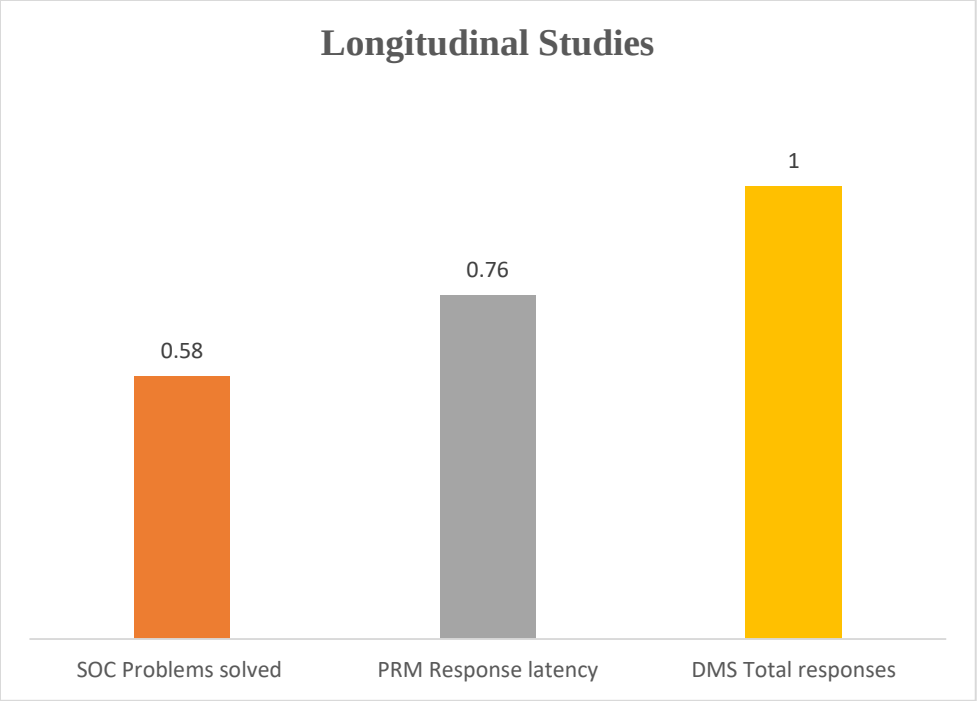

Figure 3: Comparison of the effect size (SMD) of CANTAB tests which show abnormalities in major depression before and after treatment (longitudinal samples). CANTAB: Cambridge Neuro- psychological Test Automated Battery; SOC: Stocking of Cambridge; PRN: Pattern Recognition Memory; DMS: Delayed Matching to Sample.

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Declaration of competing interests

AHY is employed by King's College London and is a Honorary Consultant psychiatrist at South London and Maudsley NHS Foundation Trust (NHS UK). He is Editor of Journal of Psychopharmacology and Deputy Editor of BJPsych Open. He has delivered paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Flow Neuroscience, Novartis, Roche, Janssen, Takeda, Noema pharma, Compass, Astrazenaca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, Sage, Neurocentrx. He is the Principal Investigator in the Restore-Life VNS registry study funded by LivaNova. He is also the Principal Investigator on ESKETINTRD3004 "An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression", "The Effects of Psilocybin on Cognitive Function in Healthy Participants", "The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)", "A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy'' (Janssen), "An Open-label, Long-term, Safety and Efficacy Study of Aticaprant as Adjunctive Therapy in Adult and Elderly Participants with Major Depressive Disorder (MDD)'' (Janssen), "A Randomized, Double-blind, Multicentre, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aticaprant 10 mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder (MDD) with Moderate-to-severe Anhedonia and Inadequate Response to Current Antidepressant Therapy'', "A Study of Disease Characteristics and Real-life Standard of Care Effectiveness in Patients with

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Major Depressive Disorder (MDD) With Anhedonia and Inadequate Response to Current Antidepressant Therapy Including an SSRI or SNR" (Janssen). He is the UK Chief Investigator for Compass COMP006 & COMP007 studies and for Novartis MDD study MIJ821A12201. His grant funding (past and present) include NIMH (USA), CIHR (Canada), NARSAD (USA), Stanley Medical Research Institute (USA), MRC (UK), Wellcome Trust (UK), Royal College of Physicians (Edin), BMA (UK), UBC-VGH Foundation (Canada), WEDC (Canada), CCS Depression Research Fund (Canada), MSFHR (Canada), NIHR (UK), Janssen (UK) EU Horizon 2020. No shareholdings in pharmaceutical companies. The other authors have no competing interests to declare.

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- Cognitive difficulties in major depression are known to persist after recovery.

- The Cambridge Neuro-psychological Test Automated Battery (CANTAB) can reliably measure cognitive function in major depression at baseline and after treatment.

- Major depression is characterised by cognitive deficits in executive functions, memory, and attention.

- Cognitive deficits measured with CANTAB 'Stocking of Cambridge', 'Pattern Recognition Memory', and 'Delayed Matching' improved following treatment.

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