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Cognitive impairments and depression: a critical review

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Cognitive impairments are core symptoms of depressive disorders. We assess the systematic reviews and meta-analysis studies published over the last 10 years (2004-2014) that address cognitive performance of depressed patients and taking into account age; clinical and demographic features; symptom severity; number of previous episodes; clinical remission; depressive subtypes and pharmacological treatment. Twelve (12) papers were included after search in international databases. In first episode depression the cognitive domains affected were psychomotor speed, attention, visual learning and memory as well as executive functions. Depressive patients in remission phase improved their performance in attention tasks although they did not achieve similar performance levels as healthy controls. Melancholic patients seem to have a different pattern of cognitive impairment compared with non-melancholic depressive patients. Patients treated with the current antidepressants perform worse in inhibition tasks, verbal fluency, and working memory scores as well as on composite scores of visual and verbal working memory. Future research should study longitudinal outcome and clinical relevance of cognitive symptoms, determine their underlying etiopathogenesis and how they impact on clinical functioning. Specifically, it would be important to analyze the ability of the new antidepressant drugs to improve affective symptoms as well as cognitive dysfunctions.

Keywords: Depression, Cognition, Cognitive Impairments, Executive Functions, Antidepressants, Remission

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Alteraciones cognitivas y depresión: una revisión crítica

Las alteraciones cognitivas constituyen un síntoma nuclear de los trastornos depresivos. Analizamos las revisiones sistemáticas y los metaanálisis publicados en los últimos 10 años (2004-2014) que estudian el rendimiento cognitivo de pacientes deprimidos teniendo en cuenta las variables de edad, características clínicas y demográficas, gravedad de la sintomatología, número de episodios previos, remisión clínica, subtipos depresivos y tratamiento farmacológico. Se incluyeron 12 trabajos tras la búsqueda en bases de datos internacionales. Las funciones afectadas en primeros episodios fueron la velocidad psicomotora, la atención, el aprendizaje y la memoria visual así como las funciones ejecutivas. Los pacientes deprimidos en fase de remisión presentan una mejoría en las tareas de atención aunque sin alcanzar los niveles de rendimiento de los controles sanos. El subtipo melancólico parece contribuir a las diferencias en los déficits cognitivos expresados. Pacientes tratados con fármacos antidepressivos clásicos obtienen peores resultados en las puntuaciones compuestas de inhibición, en las pruebas de fluidez verbal, en las puntuaciones de memoria de trabajo verbal y en las puntuaciones compuestas de memoria de trabajo viso-espacial. Futuros estudios deben explorar la naturaleza longitudinal y la relevancia clínica de los síntomas cognitivos, determinar la dirección etiopatogénica de los mismos y su impacto en la funcionalidad global. De manera particular será relevante analizar en los nuevos fármacos antidepressivos su capacidad de mejorar no solo la sintomatología afectiva sino también las alteraciones cognitivas.

Palabras clave: Depresión, Cognición, Alteraciones cognitivas, Funciones ejecutivas, Antidepressivos, Remisión

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Depression is often a long-term condition, occurring with relapses and recurrences, which tends to become a chronic disease. According to several authors cognitive impairments would be a core component of major depressive disorder (MDD).¹ Cognitive impairments in the current DSM-5 classification are one of the diagnostic criteria of depressive disorders. In some cases, the deficits found are moderate, but in most of the studies the alterations are significant. A growing number of works in the field of neuropsychology suggest that depressive patients show different alterations in executive functions (EF) and working memory, among other cognitive domains.²⁻⁴ However, the controversy on whether certain cognitive impairments would be related with difficulties in functional rehabilitation of the depressed patients remains. Residual symptoms observed in patients with response or even clinical remission, which correlate with altered or non-recovered functionality, opens up many questions regarding the role of cognition in the course and prognosis of depressive disorders in the middle and long term⁵ and therapeutic adherence.⁶

Current research attempts to relate these alterations with first episode or recurrent depression and to clarify if they disappear or not during remission phases, and consequently if some depressive disorders or subtypes would imply stable or permanent deficits. Response and clinical remission do not prevent the presence of residual symptoms.⁵ It has been suggested that some cognitive dysfunctions that do not disappear in spite of the clinical response would be related with difficulties in functional rehabilitation of depressive patients.⁷ Review of the impact of classic antidepressants or those already on the market as well as new drugs on different cognitive domains has become another promising line of research in neuroscience. Neurobiological, clinical and treatment aspects try to fit the results together based on the most recent research findings. Rock et al.,² in a systematic review and meta-analysis, analyzed 24 studies in which they evaluated cognitive impairment in different cognitive domains (EF, memory, attention and reaction time) based on the assessment battery Cambridge Neuropsychological Test Automated Battery (CANTAB). When patients with MDD were compared with healthy subjects, patients with depression showed cognitive deterioration in EF, memory and attention. Differences were not observed between both groups in reaction time. Trivedi and Greer¹ analyzed 12 works, systematic reviews and meta-analyses comparing depressed patients and healthy subjects. They concluded that there was enough evidence to support the idea of cognitive alterations in depression, mainly attention, psychomotor speed, EFs and working memory.

In regards to more specific data about neuropsychological deficit in EFs of MDD patients, two meta-analyses that show significant alteration in this domain have been recently published. One corresponds to Snyder,³ who analyzed 113

studies comparing depressive subjects with healthy controls, obtaining a total sample of 7707 participants. The results indicate that MDD was associated with poor performance in every neuropsychological measurement of EF (inhibition, mental flexibility, update of information in the verbal and visual-spatial working memory, planning, verbal fluency, processing speed and vocabulary) with effect sizes ranging from moderate to large. The second work was published by Wagner et al.,⁴ based on 15 studies with a sample of 375 patients diagnosed of unipolar depression without psychotic symptoms and under drug treatment compared with 481 healthy controls. The analysis showed that the group of depressed patients had significant impairment in response inhibition, cognitive flexibility and semantic verbal fluency and moderate deterioration in planning and organization.

Some of disparities found may be the result, as in many occasions in our setting, of the heterogeneity of the methodologies applied, with reduced samples or the fact that cognitive dysfunctions did not constitute the main outcome variable. We have proposed a critical review based on systematic reviews and meta-analyses published over the last 10 years (2004-2014) that will analyze cognitive performance of patients with depression, taking into consideration age, clinical and demographic characteristics, symptom severity, number of previous episodes, clinical remission, depressive subtypes and/or pharmacological treatment.

METHOD

A search was made in PubMed/Medline using the terms ("neuropsychological" OR "cognitive" OR "cognition" OR "cognitive impairment" OR "cognitive function" OR "executive function" OR "memory" OR "verbal fluency" OR "attention") AND ("affective disorder" OR "depressive disorder" OR "major depression"). Reviews and meta-analyses published in English between 2004 and 2014, a 10-year period, were included. A total of 316 articles were obtained and manually reviewed by two of the authors. The works with bipolar depression and samples of elderly patients were excluded. At the end, 12 works that evaluated depression and cognitive alterations in any of the variables mentioned were included (Table 1).

RESULTS

Age

The meta-analysis of Castaneda et al.⁸ analyzed 9 studies of cognitive functions in young subjects with depression. As in the studies focused on samples of adult patients with MDD, executive dysfunction was the key neuropsychological deficit, with impairments in attention deficits, deterioration

Table 1 Systematic reviews and meta-analyses on depression and cognitive impairments (2004–2014)				
Author	Year	Clinical aspects	Cognitive domains	Studies included
Porter et al. ²³	2007	Severity of depression, Melancholic subtype, Age and Pharmacotherapy	Attention, Verbal and non-verbal memory, and Executive functions	20
Castaneda et al. ⁸	2008	Severity of depression, and Anxiety disorders	Executive functions, Working memory, Verbal learning and memory	9
McDermott et al. ¹¹	2009	Severity of depression	Executive functions, Memory, and Processing speed	69
McClintock et al. ²²	2010	Severity of depression, and Number of previous episodes	Executive functions, Attention, and Memory	35
Hasselbach et al. ¹⁵	2011	Remission in unipolar depression	Attention, Executive functions Memory, and Learning	11
Wagner et al. ⁴	2012	Severity of depression, and comparison with healthy controls	Executive functions	15
Lee et al. ¹²	2012	Patients with a first depressive episode	Psychomotor speed, Attention, Working memory, Verbal learning and memory, Visual learning and memory, cognitive flexibility, Verbal fluency, and attentional flexibility	13
Bora et al. ¹³	2013	Age of onset, and comparison with healthy controls	Executive functions, Working memory, Attention, verbal and visual memory, and Processing speed	27
Rock et al. ²	2013	Acute phase of the depression and clinical remission	Executive functions, and CANTAB*	24
Snyder ³	2013	Age of patient, severity, and pharmacotherapy	Executive functions	113
Baune et al. ⁹	2014	Depressed patients ages 12 to 25 years	Executive functions, Memory, Attention, Psychomotor speed, and Processing speed	7
Trivedi et al. ¹	2014	Pharmacotherapy	Executive functions, Learning, and Memory	12

*CANTAB (Cambridge Neuropsychological Test Automated Battery): Memory, Attention and Reaction time in cognitive tasks

of short term memory and verbal work, and dysfunction in the psychomotor skills. Results about remission and cognitive dysfunction were contradictory.

Baune et al.⁹ recently published a review including 7 studies with adolescent and young adult depressed patients (from 12 to 25 years of age). When patients were compared with healthy controls, results showed neuropsychological deficits in different cognitive domains, mainly in executive function, working memory, psychomotor speed and processing, verbal fluency and visual memory. On the contrary, differences in attention and verbal learning and memory were not observed.

In the meta-analysis of Snyder³ mean age of patients predicted great deterioration in Trail Making Test (part B) as well as scores of psychomotor speed and vocabulary, controlling symptom severity and medication. However, there was no effect of age on remaining measurements.

Some studies included in the meta-analysis state that the EF deficits are sharper in elderly depressed adults although the global results do not support this findings.

Writing this manuscript, in the early stages of 2015 Vilgis et al.¹⁰ published a meta-analysis in which they concluded that there is little evidence supporting the idea of cognitive deficits in depressed children and adolescents, and that these deficits are focused on inhibition and cognitive flexibility, selective attention, and verbal working memory and verbal fluency. Equally, authors also refer that only those samples under medication performed worse than healthy controls in sustained attention tasks.

Severity of the clinical symptoms

The meta-analysis of Snyder³ showed that performance in some neuropsychological measures of EF is sensitive to

symptom severity, revealed by the existence of a positive relation between both measurements. Specifically, data relate symptom severity with greater deterioration in inhibition composite scores, mental flexibility and verbal fluency (controlling the age and medication variables). However, the effects of the severity of the current symptoms were not significant in the interference of the Stroop, Trail Making Test (part B), verbal working memory in general or in the composite scores of Digit Retention in forward order. Except for the latter test, statistical tendencies were found relating worse symptomatic presentation with poor performance in resistance to interference, cognitive flexibility and verbal working memory tasks.

In the meta-analysis of McDermott and Ebmeier¹¹ 14 studies were included. These works assessed the relationship between severity of the depressive episode according to the HAM-D or MADRS scores and performance on different neuropsychological tests. Significant negative correlations were observed with small to moderate effect between symptom severity and episodic memory ($g=0.31$), EF tasks ($g=0.32$) and processing speed ($g=0.16$) while no relation was found between the scores on HAM-D and MADRS with the semantic memory tests or visual-spatial memory.

Previous episodes

Lee et al.¹² published a meta-analysis which analyzed the cognitive symptoms specifically focused on first episodes of MDD. For the analysis, they used 13 studies with a total sample of 644 depressed subjects and 570 healthy controls. Results showed that cognitive functions affected in these patients were psychomotor speed ($g=0.48$), attention ($g=0.36$), learning and visual memory ($g=0.53$) and EFs. In the latter domain, attention switching ($g=0.22$), verbal fluency ($g=0.59$), and cognitive flexibility ($g=0.53$) were worse in depressed patients compared to healthy subjects. Remission of symptoms, hospitalization of the patient, use of antidepressants, age and education level significantly contributed to the heterogeneity in the effect sizes of cognitive function.

In the meta-analysis of Snyder³ contradictory results were seen in regards to the role of the previous episodes due high heterogeneity of the samples and reduced number of studies. In this meta-analysis, author calls to increase the studies on the role of the previous episodes in executive functions, as well as the importance of investigate the interaction between age of onset and previous depressive episodes.

Remission

Bora et al.¹³ performed a meta-analysis of 27 studies with a sample of 895 depressed subjects and 993 healthy

controls. When both groups were compared the "global cognition" index (mean of the effect sizes in each one of the cognitive domains) was significantly worse in patients with remitted MDD compared with healthy controls ($d=0.50$). Similar results were found when performance was assessed based on type of cognitive domain. The healthy control group perform better in every cognitive domain ($d=0.39$ to 0.59).

According to Douglas and Porter,¹⁴ after an analysis of 30 studies on cognitive alterations in MDD, memory and verbal fluency improved once remission was achieved while attention and EFs remained deteriorated during the MDD recovery treatment phase. However, two studies showed that depressed patients in remission phase improve their scores in attention tasks, without reaching the performance levels of the healthy controls.

Rock et al.,² analyzed six studies comparing differences in EFs, memory and attention, between patients with MDD in remission and healthy subjects, data suggested moderate significant deficits in the group of patients with remission in the EFs ($d=-0.53$ to -0.61) and attention tests ($d=-0.52$). Regarding memory, they observed a moderate improvement in the group of remitted patients ($d=-0.22$ to -0.54).

Hasselbalch et al.¹⁵ made a review of 11 studies that compared subjects with depression in remission ($n=500$) with healthy subjects ($n=471$). Results indicated that performance on tests measuring global cognition, attention, memory and EF was poorer in at least one of the tests that evaluated each domain in the depression group in 9 out of the 11 studies. When different sociodemographic and clinical variables were considered, results on the role of remission in the cognitive functions changed. The data on the effects of remission in the elderly were different from those obtained in the adult population, improvement was only significant in psychomotor speed.¹⁴ According to the moment when the episode appears, a characteristic of the late onset episodes is high cognitive impairment.¹⁵ This finding is consistent with the work of Bora et al.¹³ in which euthymic patients with late onset show a more severe alteration in global cognition ($d=0.64$) and in specific domains ($d=0.42$ to 1.10), mainly in verbal memory. In the same work, data reported correlate early onset of the disorder with less deterioration in both scores ($d=0.21$ to 0.54). In accordance with Hasselbalch et al.,¹⁵ performance in cognitive tasks is reduced in those patients in remission with recurrent depression, this decrease is more pronounced after the third episode. However, the data should be considered with caution due to the risk of methodological biases that were not taken into account in the analysis.¹⁵

Subtypes of MDD

The nature of the clinical spectrum of the depressive disorder is heterogeneous. Consequently, attempts to char-

acterize the specific cognitive profiles in accordance with the clinical manifestation have not been conclusive up to now. However, severity of the depression and specifically the melancholic subtype seems to contribute to the differences in the cognitive deficits expressed in depression when the data are analyzed longitudinally.^{16,17}

The meta-analysis of Snyder³ studied individual differences between MDD subtypes, with inconsistent results. Two studies^{18,19} found that patients with melancholic MDD performed significantly worse in cognitive flexibility tasks than patients with non-melancholic MDD. On the other hand, deterioration was not observed in measurements of planning and the results on psychomotor deterioration were not conclusive. Similarly, another study referenced²⁰ in the meta-analysis found worse performance in patients with melancholic MDD compared with healthy participants in tests measuring cognitive flexibility (Trail Making Test-part B and the Wisconsin Card Sorting Test), and verbal working memory (digit retention in reverse order). In patients diagnosed of non-melancholic MDD, poor performance was only observed in the Wisconsin Card Sorting Test. However, Snyder pointed out that a third study²¹ found that the patients with non-melancholic MDD showed greater deterioration on Stroop test than healthy subjects that was not present in the melancholic MDD group. When the two groups of patients were compared, no significant differences were found. These data are inconsistent with those published by Roca et al.¹⁶ which showed that patients with melancholic depression, when compared with non-melancholic patients, performed worse in executive function tests.

Drug treatment

Cognitive disorders do not seem to be a mere artifact of the treatments. Different studies have suggested that some extended treatments with tricyclic and tetracyclic antidepressants^{22,23} could have a negative impact on cognition. Given the lack of studies with random allotment to treatment, it is difficult to compare and explain the outcomes, but the study of the action mechanisms of the drugs used up to now have led some expert authors to wonder about their positive action on cognition.³ Only three studies that addressed cognitive alterations before and during treatment with antidepressants have found some differences: improvement was observed in the Stroop, but the recorded effect size was moderate. In accordance with Snyder³ patients treated with psychotropic drugs obtained worse results in the composite scores of inhibition on the Trail Making Test (part B), on the verbal fluency tests, on the verbal working memory scores and on the composite scores of visual-spatial working memory. On the other hand, even though a tendency in the same direction was observed in all the measurements, there were no significant effects of the medication on interference assessed with the Stroop, cognitive flexibility

measured with the Wisconsin Card Sorting Test (WCST), or in the composite scores of manipulation of the verbal working memory. In spite of the association of the use of medication with lower performance in these cognitive domains, significant deficits were also observed in the group of patients without drug treatment. These results about the effect of medication were calculated controlling the variable "symptom severity". However, clinical variables such as "duration of treatment" or "grade of resistance to treatment," were not controlled so that there may be confounders that could bias the results.

In the work of Rock,² the effect of medication was also assessed for EF, memory and attention. Data of eight studies that compared depressed subjects without drug treatment with a control group of healthy subjects were analyzed. The results suggested that depressed patients had moderately significant deficits in one of the tasks within the EFs ($d=-0.46$), in two memory tasks ($d=-0.33$ to -0.36) and in attention task ($d=-0.59$).

In the meta-analysis carried out by Wagner et al.⁴ the impact of antidepressive treatment on performance of cognitive flexibility was analyzed with the Stroop interference test. Only 3 of the 15 studies met the inclusion criteria for this part of the analysis, which showed a significant improvement in the post-treatment performance compared with pre-treatment condition.

The use of antidepressants was also associated with low performance in tasks evaluating working memory and verbal learning in the meta-analysis of Lee et al.¹² However, it was not specified if the correlation with the antidepressant treatment reflected the severity of depressive symptoms or an effect of the drug treatment.

CONCLUSIONS

Cognitive symptoms, derived from alterations in some of the cognitive functions, are a central and core characteristic of depressive disorders. Research in this topic has multiplied in recent years, in spite of the difficulties for an adequate neuropsychological assessment and the variability of the measurements used. With currently available data it is complex to infer if the impairments detected are the result of specific dysfunctions or the impact on a wide ranging domains.

In accordance with the available systematic reviews and meta-analyses that we have analyzed, age of the patients predicted great impairment in the Trail Making Test (part B) and the composite scores of psychomotor speed and vocabulary. Furthermore, performance in some neuropsychological measurements of executive functions is sensitive to severity of the depression symptoms. The cognitive functions affected in patients with first episodes were psychomotor

speed, attention, learning and visual memory as well as executive functions. Depressed patients in remission phase showed improvement in attention tasks, although they did not achieve the performance levels of the healthy controls. It was not possible to infer from these results if each depressive episode increases the risk of cognitive deficits, there being a substantial debate on whether the clinical episodes would leave a "scar."²⁴ Neuroimaging studies defend that the number of episodes and duration of the disease would be associated to structural atrophies in areas such as the hippocampus.^{25,26}

In regards of the heterogeneity of affective disorders, melancholic depression appears to contribute to the differences in the cognitive deficits expressed,¹⁶ at the expense of the results of the studies with larger samples and longer follow-ups. Finally, patients treated with some antidepressant drugs marketed up to now obtained worse results in the composite scores of inhibition, in the Trail Making Test (part B), in the verbal fluency tests, in the verbal working memory scores and in the composite scores of visual-spatial working memory. Few studies have shown that classic antidepressant drugs have been effective increasing cognitive function or addressing cognition as main outcome variable.. Some classical antidepressants widely used up to now can clearly worsen the cognitive function.

Future studies, in line with previous works¹¹, should study the longitudinal nature and clinical importance of the cognitive symptoms and alterations in MDD. Furthermore, it would be recommendable to determine their etiopathogenic direction, their early detection and management, their impact on global functionality, and specifically to analyze the new antidepressant drugs –as well as those in the last development phases– capacity to improve not only affective symptoms but also the cognitive dysfunctions. This is the only way that we will be able to advance in a useful direction to understand the complex relation between depression and neuropsychological functioning for early detection, early intervention and better management and prognosis of the depressive disorders.

CONFLICT OF INTERESTS

In the last twelve months, M. Roca has received funding for research projects from the Instituto de Salud Carlos III and the European Union as well as fees for participation in Continuing Medical Education or consulting from Ferrer, Janssen, Pfizer and Lundbeck. J. García-Campayo has received, in the last twelve months, funding for research projects from the Instituto de Salud Carlos III and fees for participation in the Continuing Medical Education or consulting from Eli Lilly, Pfizer, Rovi and GSK. The rest of the authors declare they have no conflict of interests.

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