

Carla Gramaglia¹
 Francesco Pietrini²
 Patrizia Zeppegno^{1,3}

¹ Psychiatry Institute, Department of Translational Medicine, Università del Piemonte Orientale, Novara

² Department of Neuroscience, Psychology, Drug Research and Child Health, Section of Neuroscience, University of Florence, Florence, Italy

³ SC Psichiatria, AOU Maggiore della Carità Hospital, Novara Carla

SYMPTOMS OF DEPRESSION: "HOT" AND "COLD" COGNITION

Abstract

Objectives: The central role of cognitive deficits in depression is well established and represents a primary mediator of the negative consequences of this disorder in both human and economic terms. The aim of the present review is to provide an up-to-date overview of current knowledge on the cognitive aspects of depression with particular focus on their clinical-therapeutic role.

Materials and methods: English language and peer-reviewed publications were obtained by searching PubMed/Medline database using the keywords "depression" or "depressive" paired with "cognition", "cognitive", "cold", "hot", "deficit", and "executive function".

Results: Recent studies have identified different cognitive systems that, when dysfunctional, play a crucial role in the onset and maintenance of depression: cognitive functions that are independent of emotional state ("cold" cognition) and cognitive regulation of emotional states ("hot" cognition). These systems develop an interaction between cognition and affectivity termed "affective cognition", which is frequently dysfunctional in individuals with depression.

Conclusions: Cognitive symptoms are increasingly the focus of clinical and scientific debate on depression, not only for their diagnostic utility, but also for their importance in the prognosis, therapy and rehabilitation of this disorder.

Key words: Depression, deficit, cognitive, affectivity, cognition, bias, antidepressants

Introduction

Depression is a severe, chronic syndrome with significant impact on functioning and quality of life, and is the leading cause of disability worldwide ^{1 2}. Major depression varies considerably in terms of clinical presentation and response to therapy, and includes a broad range of different phenotypes ³⁻⁶. However, available literature indicates that cognitive impairment associated with depression is the main driver of negative consequences in both human and economic terms ^{7 8}.

The key role of cognitive dysfunction in depression has been amply demonstrated ⁹⁻¹², which is reinforced by current diagnostic systems ¹³. The Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. (DMS-5), in fact, includes cognitive dysfunction as a diagnostic criterion of major depression by itself (criterion 8: diminished ability to think or concentrate, or indecisiveness, nearly every day) and as a component of other cardinal symptoms (Criterion 2: markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day; Criterion 5: psychomotor agitation or retardation nearly every day) ¹³.

Cognitive depressive symptomology is a subject of clinical and scientific debate not only for its diagnostic value, but also for its importance in prognosis, therapy and rehabilitation ¹⁴. Indeed, the available evidence indicates that the cognitive dimension of major depression is one of the main indicators of vulnerability ¹⁵, clinical course ¹⁶, response to therapy (both antidepressant ^{17 18} and psychotherapy ¹⁹) and functional recovery ⁷.

Correspondence

Patrizia Zeppegno
 patrizia.zeppegno@med.uniupo.it

In regard to depression treatment, for example, some antidepressants have a demonstrated efficacy not only on the affective aspects of major depression, but also on cognitive depressive symptoms (especially those involving executive functions and emotional processing)²⁰⁻²². In particular, current research has focused on selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI), with the latter showing superiority over the former in terms of efficacy on cognitive aspects²³⁻²⁴. Other non-pharmacological treatments such as cognitive-behavioural therapy and cognitive remediation are also considered promising approaches in the treatment of major depression²¹.

Over the last two decades²⁵, several cognitive systems have been identified that play a crucial role in the onset and maintenance of depression: executive cognitive functions that are independent of the emotional state ("cold" cognition which functions in control of cognition) and affective cognitive processes ("hot" cognition which functions in elaboration of emotionally-relevant stimuli)¹⁰⁻²⁶. These two systems develop an interaction between cognition and affectivity ("affective cognition") that guides thought and behaviour in the response to emotionally relevant stimuli¹²⁻²⁶⁻²⁸. It is this interaction that appears dysfunctional in subjects with depression²⁹.

The aim of the present review is to provide up-to-date information on the cognitive aspects of depression, with focus on the alterations of executive functions ("cold" cognition) and of the cognitive regulation of emotions ("hot" cognition).

Materials and methods

A review of the literature was performed searching PubMed and electronic data base through July 2015 for studies published in English at any time prior to the search date. Searches were conducted using the keywords "depression" or "depressive" paired with "cognition", "cognitive", "cold", "hot", "deficit", and "executive function" (e.g. "Depression/diagnosis"[Mesh] OR "Depression/physiopathology"[Mesh] OR "Depression/psychology"[Mesh] AND "cognition"[Mesh]). An initial screening was conducted by examining titles to eliminate studies that clearly did not meet the inclusion criteria. Searches excluded bipolar, psychosis, stroke, Parkinson's disease, Alzheimer's disease, and post-partum depression. The remaining abstracts were reviewed to identify studies, systematic reviews, and meta-analyses evaluating cognition in patients with depression. Selection criteria

were: original neuropsychological investigations with a healthy control group and use of tasks investigating cognitive function, emotional processing, or reward/punishment processing or systematic reviews and meta-analyses. If an article appeared likely to meet the inclusion criteria the full text was obtained. In addition, the reference lists of included articles, and articles citing included articles, were screened for any studies missed in the database search process. We focused on studies reported in the past 15 years but also included commonly referenced and highly regarded older publications. Whenever the data obtained by a single study were later included in a meta-analysis we choose to refer to the results of the meta-analysis rather than to the results of the original study. Review articles and book chapters are cited to provide readers with more details and additional references.

"Cold" cognition in depression

Executive functions, classically belonging to "cold cognition" or independent of affectivity, are represented by systems with inhibitory action (suppression of some answers to give priority to others), information management (working memory) and adaptation to external requests (modulation of response and addressing attention)³⁰. The correct combination of these systems represents the basis for organisation of higher order executive functions such as problem solving and planning behavioural responses²⁵.

In theory, "cold" cognitive functions can be evaluated with tests that involve emotionally and motivationally neutral stimuli. On the basis of this principle, over the years, a series of neuropsychological instruments have been developed that include the Digit Symbol Substitution Test (DSST), the California Verbal Learning Test (CVLT), the Wisconsin Card Sorting Test (WCST), the Trail-Making Test (TMT) and the Stroop Colour-Word Interference Test (SCWT)¹¹. These instruments have been used in a number of neuropsychological studies to investigate the principal domains of "cold" cognition in depression (including working memory, selective attention, response inhibition, cognitive flexibility, motor inhibition and verbal fluency), which have highlighted that there are important deficits in these functions in depression⁹. The results of the present review on cold cognition in depression are summarized in Table I. In two recent meta-analyses of the available neuropsychological studies, the degree of compromise of cognitive function in depression was demonstrated to have little

correlation with the severity of symptoms, underlining the importance of these deficits even in the subclinical phases and in remission^{35 42}.

Through neuropsychological research and the recent availability of advanced imaging techniques, the attention on the cognitive symptoms of depression has focused on the neural basis of these dysfunctions^{29 46}. Neuroimaging studies of “cold” cognitive processes have investigated a series of domains (including working memory, verbal fluency, inhibition of response and selective attention) using various types of stimulation or tasks (Stroop task, Go/No-Go, continuous performance task, etc.) and functional imaging techniques⁴⁷. The results of this research seem to indicate dysfunction in areas implicated in “top-down” cognitive control in the processing of stimuli, which involves prefrontal cortex (PFC), anterior cingulate cortex (ACC) and insula^{29 46-48}. Patients with depression, moreover, show a reduced deactivation of the network of neural areas that regulate the resting state (default mode network; DMN), a function that involves cerebral glutamatergic activity^{49 50}. The dysfunctional relationship between inefficiency of prefrontal areas that control cognition and altered deactivation of the DMN appears to be more severe in patients with greater degree of rumination⁵¹, suggesting a central role of attention and working memory deficits in depression⁵²⁻⁵⁴.

“Hot” cognition in depression

In the scientific literature, the term “hot” cognition refers to the cognitive functions involved in elaboration of emotionally relevant stimuli^{47 55}. The results of the present review on “hot” cognition in depression are summarized in Table II. Executive functions are systematically influenced by emotions in an interaction known as cognitive affective bias (CAB). In depression, studies of CAB have revealed deficits in elaboration of affective stimuli with positive valence and preferential processing of those with negative valence^{10 12 26 55 78 91}. This emotional imbalance favouring stimuli with negative valence (referred to as “negative bias”) alters many aspects of cognitive functioning in patients with depression, including perception, attention, learning and working memory^{55 91 92}. Several authors believe that affective cognitive bias has a central role in the development, maintenance and treatment of depression^{10-12 26}.

The main neuropsychological studies on CAB in major depression have shown that depressed patients tend to remember negative information bet-

ter than positive information^{56 66 67 71} and to interpret social signs, such as facial expressions, in a more negative (or less positive) manner than healthy subjects^{68 70 74 76 93 94}. Moreover, individuals with depression show persistent susceptibility to distractions by emotionally negative stimuli, which acquire an emotional relevance that impairs normal and effective decision-making^{95 96}. This type of functioning appears to be in complete contrast with that of healthy subjects, who show an attentive bias towards positive-valenced stimuli^{68 72 74 77 81 97}. As a consequence, patients with depression have a decreased ability to divert attention from negative stimuli than healthy subjects^{52 53 63 76 88}.

Another recently studied domain of “hot” cognition in major depression involves reward and punishment⁹⁸. The significant alteration in the ability to experience gratification, satisfaction and pleasure (anhedonia) is one of the cardinal symptoms for diagnosis of major depression¹³. Studies in this area have reported that depressed patients, compared with healthy subjects, are hypersensitive to failure and to negative outcomes of neuropsychological tests^{61 84 99} and, in contrast, relatively insensitive to rewards^{80 100 101}. Evidently, the dysregulation of the value reward/punishment attribution to emotional stimuli (or of the positive and negative reinforcement systems) negatively affects the development of learning processes and behavioural strategies that are appropriate to the context^{73 79}.

At present, there are no well validated techniques for neuropsychological evaluation of the cognitive processes that regulate emotion, and most of the available information on “hot” cognition has been obtained from neuroimaging studies^{29 48}. These investigations have demonstrated that the dysfunctions in “hot” cognition involved in the regulation of emotion can be attributed to an abnormal functioning of a network of several cerebral areas^{10 29 47 98 102}. One area of research using experimental procedures to assess cognitive performance in depressed subjects (especially memory and attention) in the presence of distracting stimuli (Emotional Go/No-Go task, Emotional Stroop task, etc.), revealed hypofunctioning of the dorso-lateral prefrontal cortex (DLPFC), medial cortex and ACC^{95 103 104}. Depressed patients show neuro-functional alterations compared with healthy subjects even in processing of emotionally relevant images. In particular, an increased activation of the amygdala when viewing emotional images with strong negative valence that seems to correlate with the severity of symptoms, has been found in depression^{105 106}.

Table I. Cold cognition in depression: summary of the main findings.

Study	Test	Results
Alexopoulos et al., 2000 ³¹	Mattis Dementia Rating Scale (DRS)	Correlation between performance on initiation/perseveration tasks and relapse/recurrence of depression in subjects aged > 65 years
Majer et al., 2004 ³²	Dual auditory/visual divided attention task of the Test batterie zur Aufmerksamkeitsprüfung (TAP)	Increased risk of relapse in patients with impaired divided attention at discharge
Castaneda et al., 2008 ³³	Trail Making Test A and Digit Symbol-Coding, California Verbal Learning Test-second edition (CVLT-II)	Younger age at depression onset is associated with more impaired executive functioning. Young adults with a lifetime history of depression show mild verbal learning deficits
Herrera-Guzman et al., 2008 ³⁴	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Depressed patients with good response to bupropion show low pre-treatment levels of mental processing speed and visual memory
McDermott & Ebmeier, 2009 ³⁵	Meta-analysis	Significant correlations between depression severity and executive function impairment, especially for processing speed and episodic memory alterations
Herrera-Guzman et al., 2010 ²³	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Remitted patients with depression show deficits in planning, sustained attention, working memory, verbal and visual memory. SNRI show higher efficacy in treating verbal and visual memory impairment than SSRI
McLennan & Mathias, 2010 ¹⁸	Meta-analysis	Positive correlation between baseline executive function performance and response to antidepressant treatment
Hasselbalch et al., 2011 ³⁶	Systematic review	Remitted patients with major depression show impairments of executive function, memory, and sustained/selective attention
Hermens et al., 2011 ³⁷	Trail-Making Test, part B (TMT B), Rey-Osterrieth Complex Figure Test (ROCF), Rey Auditory Verbal Learning Test (RAVLT)	Poor cognitive flexibility, visual memory, verbal learning and memory in patients with current depressive episode.
Maalouf et al., 2011 ³⁸	Stockings of Cambridge task (SOC), Rapid Visual Processing task (RVP)	Adolescents with current depression show more impaired executive function and sustained attention compared to adolescents with remitted depression and healthy controls
Lee et al., 2012 ³⁹	Meta-analysis	Patients with first-episode depression perform significantly worse than healthy controls in cognitive task involving all aspects of executive function (especially attention, psychomotor speed, visual learning and memory)
Wagner et al., 2012 ⁴⁰	Meta-analysis	Impaired verbal fluency, cognitive flexibility, and response inhibition in depressed patients compared to healthy controls
Baer et al., 2013 ⁴¹	Montreal Cognitive Assessment (MoCA)	Depressive symptomatology is negatively associated with level of cognitive status one year after retirement
Snyder, 2013 ⁴²	Meta-analysis	Significantly impaired performance for depressed patients, compared to healthy control, on all neuropsychological measures of executive function. Deficits may be greater in patients with more severe current depression symptoms, and those taking psychotropic medications. Evidence for effects of age was weaker.
Boelen et al., 2014 ⁴³	Sentence Completion for Events from the Past Test (SCEPT)	Reduced memory specificity is associated with concurrent and later depression in a sample of university students
Li et al., 2014 ⁴⁴	Wechsler Adult Intelligence Scale-III, Digit Span subtest (forward and backward), computerized paradigm to test prospective memory	Prospective memory (PM) performance of individuals with high depressive symptomatology (HDS) was significantly poorer than that of low depressive symptomatology participants (LDS). HDS participants were restricted in their allocation of attentional resources to support PM.
Lin et al., 2014 ⁴⁵	Rey Auditory Verbal Learning Test (RAVLT)	Higher depressive symptoms scores are associated with lower delayed recall and recognition.

Table II. Hot cognition in depression: summary of the main findings.

Study	Test	Results
Mackinger et al., 2000 ⁵⁶	Autobiographical memory task	Women with remitted depression retrieve significantly more categoric descriptions when responding to negative cue words
Mogg et al., 2000 ⁵⁷	Attentional faces dot-probe task	Depressed patients show increased attention toward sad faces
Neshat-Doost et al., 2000 ⁵⁸	Attentional words dot-probe task	No evidence of attentional bias, either towards depression-related words or threat words in depressed patients
Dozois & Dobson, 2001 ⁵⁹	Self-Referent Encoding Task	Depressed patients endorse and recall less positive information compared to anxious and healthy subjects
Murphy et al., 2001 ⁶⁰	Computerized decision-making task	Depressed patients show reduced risk adjustment in response to positive reinforcement
Murphy et al., 2003 ⁶¹	Visual discrimination and reversal learning task with negative feedback	Depressed patients show increased tendency to switch responding towards incorrect stimulus following negative reinforcement
Bhagwagar et al., 2004 ⁶²	Facial expression recognition task	Subjects with a history of depression show a selectively greater recognition of expressions of fear compared to subjects with no history of depression
Gotlib et al., 2004 ⁶³	Faces dot-probe task	Depressed patients show selective attention to sad faces compared to angry and happy faces
Joormann & Siemer, 2004 ⁶⁴	Autobiographical memory and mood regulation task	Reduced ability of positive autobiographical memory to regulate negative mood in depressed patients
Leppanen et al., 2004 ⁶⁵	Facial expression recognition task	Depressed patients show reduced speed in recognizing neutral faces and increased tendency to interpret them as either happy or sad
Hayward et al., 2005 ⁶⁶	Facial expression recognition and emotional words task	Increased negative bias in the recognition of faces and memory for emotional words after tryptophan depletion
Raes et al., 2005 ⁶⁷	Autobiographical Memory Test	Depressed subjects show reduced specificity of autobiographical memory
Joormann & Gotlib, 2007 ⁶⁸	Faces dot-probe task	Depressed patients show selective attention to sad faces and absence of positive bias towards happy faces
Joormann et al., 2007 ⁶⁹	Autobiographical memory and mood regulation task	Positive autobiographical memory fails to regulate negative mood of depressed patients that, on the contrary, seems to worsen after the recall
Gollan et al., 2008 ⁷⁰	Facial expression recognition task	Major depression is associated with reduced speed in the recognition of sad facial expressions and with negative bias towards interpreting neutral facial expressions as sad
Harmer et al., 2009 ⁷¹	Battery of emotional processing tasks	Depressed patients show reduced recognition of positive facial expressions, reduced speed of response to/memory of positive self-relevant words
LeMoult et al., 2009 ⁷²	Facial expression recognition following negative mood induction	Patients with recurrent major depression show reduced ability in recognizing happy faces
Chase et al., 2010 ⁷³	Probabilistic selection task	Depressed patients show a blunting of the training phase of the learning task specifically related to the severity of anhedonia
Milders et al., 2010 ⁷⁴	Facial expression recognition task	Patients with major depression show higher accuracy and higher response bias than controls for sad expressions
Anderson et al., 2011 ⁷⁵	Facial expression recognition task	Remitted patients show increased emotions recognition due to increased response bias. Currently depressed patients show reduced emotion recognition accuracy
Sterzer et al., 2011 ⁷⁶	Variant of binocular rivalry continuous flash suppression	Shorter suppression of sad faces and longer suppression of happy faces in depressed patients compared to healthy controls

(continued)

Table II - follows.

Study	Test	Results
Atchley et al., 2012 ⁷⁷	Attentional words and pictures task	Absence of the normal detection bias for positive picture stimuli and person-referent words in depressed subjects
Hu et al., 2012 ⁷⁸	Word-face Stroop task	Differently from what happens in healthy controls, depression-related distractor words induce significant emotional conflict to positive target faces in depressed patients
Kunisato et al., 2012 ⁷⁹	Probabilistic learning task	Depressed patients show a reward-based decision making deficit and an impaired variability of action selection compared to non-depressed subjects
Treadway et al., 2012 ⁸⁰	Effort Expenditure for Rewards Task	Depressed patients are less willing to expend effort for rewards than healthy controls
Everaert et al., 2013 ⁸¹	Spatial cueing task, scrambled sentences test, incidental free recall task	Subclinically depressed patients show negative bias in attention that has an indirect effect on memory via a negative bias in interpretation
Kruijt et al., 2013 ⁸²	Leiden Index of Depression Sensitivity – Implicit Association Test	Cognitive reactivity and implicit self-depressed associations are significantly associated with depression incidence in a sample of never-depressed individuals
Romero et al., 2013 ⁸³	Scrambled sentence test, lexical decision task, self-referent incidental recall task	Increased recall of negative self-referent words is predicted by increased negative cognitions at both explicit and automatic level of information processing in remitted depression
Schroder et al., 2013 ⁸⁴	Modified Eriksen flanker task	Depressive symptoms are associated to poorer post-error accuracy in difficult reversal blocks in a sample of young adults
Orgeta, 2014 ⁸⁵	Facial expression recognition task	Older adults with mild depressive symptoms show reduced ability to recognize facial expressions of fear and anger
Takano et al., 2014 ⁸⁶	Think-aloud and time-estimation tasks	Negative thinking is associated with greater judgement errors in females subjects as compared to males with similar levels of depressive symptoms
Vanderlind et al., 2014 ⁸⁷	Emotional cuing task	Less cognitive control over negative stimuli predicts increased depression symptoms in a sample of young adults
Yoon et al., 2014 ⁸⁸	Working memory task for emotionally-relevant words	Depressed patients show impaired ability to remove irrelevant emotional material from working memory associated with increased rumination
Pfeiffer et al., 2015 ⁸⁹	Cognitive reactivity assessment after negative mood induction	Change in depressive thinking in response to negative mood induction is negatively associated with future depression in depressed subjects
Remmers et al., 2015 ⁹⁰	Judgment of Semantic Coherence Task	Depressed patients show impaired intuition compared to healthy control participants. Negative affect accounts for the association between rumination and impaired intuition

However, the most widely used functional neuroimaging method to investigate the elaboration of emotional stimuli in depression entails the measurement of the response of patients who are shown emotionally relevant facial expressions¹⁰⁷. Even these types of studies have consistently reported the presence of an hyperactivation of the amygdala and of an altered connectivity between the amygdala and the ACC in depressed subjects who are shown facial expressions with emotionally negative valence^{94 107-109}. As described above, reward processing of emotional

stimuli is another system that appears to be altered in depression⁹⁸. Elaboration and processing of stimuli with reward/gratification valence is traditionally studied using techniques that involve winning money or obtaining social gratification^{110 111}. These types of methods are designed to evoke the activity of neural areas involved in evaluation of reward, which include the ventral striatum (caudate and putamen), orbital frontal cortex (OFC), mPFC, ACC and its main connections (including the amygdala)¹⁰. Reduced activation of the caudate and Nucleus Accumbens has been found in

depression before and after receiving an award¹¹²⁻¹¹⁴. This phenomenon appears to correlate with the disease status and to be reversible after antidepressant treatment^{79 114}. Lastly, as for “cold” cognition, cognitive elaboration of affective stimuli seems to have a role in altered activation of the DMN¹¹⁵.

Discussion

From 25% to 50% of patients with major depression present with significant compromise in at least one cognitive domain¹¹⁶. The most frequently altered cognitive functions during the course of depression are working memory, attention and rate of elaboration of stimuli^{9 39}. Such dysfunctions are significantly associated with the frequency of relapse and the duration of disease¹¹⁷ and are often present before the onset of depression¹⁵ and in the remission phase^{35 42 118}. Moreover, cognitive alterations have the greatest impact on patient functioning in major depression⁸. This indicates that cognitive deficits may be considered more as a central element in major depression rather than just secondary phenomena¹¹.

As previously mentioned, subjects with depression have a decreased ability to distract attention from negative stimuli than healthy individuals^{52 53}. This deficit in modulating attention of emotionally relevant information seems to be correlated not only with severity and duration of depressive symptoms, but also with pathological cognitive strategies such as rumination^{12 52}. Rumination is a type of recurrent thinking which is self-centred and focused on negative content and which is able to “block” attention on the latter, with a rigid and unproductive use of cognitive resources that interfere with normal cognitive performance and planning of adequate behavioural strategies⁵². Research on the cognitive aspects of depression has indicated that the presence of rumination has important clinical relevance since it can predict episodes of recurrent depression in remitted subjects⁵².

Even if for simplicity the mentioned dysfunctional cognitive aspects of depression are divided into “emotionally independent” and “emotionally dependent”, there is no reason to consider “hot” cognition and “cold” cognition as two completely separate systems^{12 28}. On the contrary, current research on the pathophysiology of major depression is increasingly focused on the interaction between cognition and affective processes, which is referred to as affective

cognition^{10 26 28}. Studies on affective cognition aim to clarify, for example, how higher order cognitive functions can modulate the elaboration of emotional stimuli (cognitive control) and how processing of emotional stimuli can influence cognitive performance in subjects with depression^{28 53 97}.

From this point of view, major depression is characterised by an excessive influence of negative emotional stimuli on executive functions (“bottom-up” dysfunction), with a distractive effect on attention, memory and behavioural planning that is at the basis of cognitive deficits⁹⁵. At the same time, the reduced ability of “cold” cognitive systems to inhibit response to negative emotional stimuli (“top-down” dysfunction) is a source of negative interpretation and attribution bias which in turn represents a maintaining factor for depression^{119 120}.

From a neurofunctional standpoint, such alterations correspond to a dysfunction of cerebral areas involved in the cognitive and emotional elaboration of stimuli^{29 48}. In particular, as a confirmation of the coordinated functioning of “hot” and “cold” cognition, an alteration of the reciprocal interaction between the PFC and amygdala has been found in depression during regulation of emotion¹²¹, consisting in a lack of deactivation of the amygdala (“bottom-up” dysfunction)¹²²⁻¹²⁴ and hypofunctioning of the DLPFC (“top-down” dysfunction)¹²⁵.

Conflicts of interest: none.

Conclusions

In conclusion, studies on affective cognition have allowed for the development of a single model of reciprocal dysregulation for the cognitive processes in depression²⁷ that integrates traditional psychological theories about dysfunctional schemes¹²⁶ with neuropsychology/neuroimaging data, and involves both “bottom-up” affective bias and “top-down” cognitive bias^{28 127}. This view also has important therapeutic implications. In fact, while the efficacy of antidepressants on cognitive symptoms in depression appears to involve normalisation of serotonergic, noradrenergic and dopaminergic dysregulation at the basis of the “bottom-up” dysfunction of affective cognition (or “hot” cognition), the efficacy of psychotherapeutic strategies with cognitive reinforcement and/or rehabilitation is based on recovery of “top-down” cognitive control of negative emotions (or “cold” cognition)^{10 12 26 128 129}.

Take home messages for psychiatric care

- Depression is a severe, chronic syndrome with significant impact on functioning and quality of life, and is the leading cause of disability worldwide. Besides its diagnostic value, cognitive impairment associated with depression is relevant as far as vulnerability, course, prognosis, therapy and rehabilitation are concerned
- From 25% to 50% of patients with major depression present with significant compromise in at least one cognitive domain, including working memory, attention and rate of elaboration of stimuli
- Even if for simplicity the dysfunctional cognitive aspects of depression are divided into "emotionally independent" and "emotionally dependent", "hot" cognition and "cold" cognition are not two completely separate systems, but rather depend on the relationship and interaction between cognition and affective processes, which is referred to as affective cognition
- Studies on affective cognition have allowed the development of a single model that integrates traditional psychological theories about dysfunctional schemes with neuropsychology/neuroimaging data, involving both "bottom-up" affective bias and "top-down" cognitive bias
- The efficacy of antidepressants on cognitive symptoms in depression appears to involve the neurotransmitter systems at the basis of "bottom-up" dysfunction of affective cognition (or "hot" cognition), while the efficacy of psychotherapeutic strategies with cognitive reinforcement and/or rehabilitation is based on recovery of "top-down" cognitive control of negative emotions (or "cold" cognition)

References

- 1 World Health Organization. *The global burden of disease. 2004 update*. Geneva: WHO 2008.
- 2 Collins PY, Patel V, Joestl SS, et al. *Grand challenges in global mental health*. Nature 2011;475:27-30.
- 3 Rush AJ. *The varied clinical presentations of major depressive disorder*. J Clin Psychiatry 2007;68:4-10.
- 4 Belmaker RH, Agam G. *Mechanisms of disease: major depressive disorder*. N Engl J Med 2008;358:55-68.
- 5 Rhebergen D, Lamers F, Spijker J, et al. *Course trajectories of unipolar depressive disorders identified by latent class growth analysis*. Psychol Med 2012;42:1383-96.
- 6 Fried EI, Nesse RM. *Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR*D study*. J Affect Disord 2014;172C:96-102.
- 7 Jaeger J, Berns S, Uzelac S, et al. *Neurocognitive deficits and disability in major depressive disorder*. Psychiatry Res 2006;145(1):39-48.
- 8 Buist-Bouwman MA, Ormel J, de GR, et al. *Mediators of the association between depression and role functioning*. Acta Psychiatr Scand 2008;118:451-458.
- 9 Austin MP, Mitchell P, Goodwin GM. *Cognitive deficits in depression: possible implications for functional neuropathology*. Br J Psychiatry 2001;178:200-6.
- 10 Elliott R, Zahn R, Deakin JF, et al. *Affective cognition and its disruption in mood disorders*. Neuropsychopharmacology 2011;36:153-82.
- 11 McIntyre RS, Cha DS, Soczynska JK, et al. *Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions*. Depress Anxiety 2013;30:515-27.
- 12 Roiser JP, Sahakian BJ. *Hot and cold cognition in depression*. CNS Spectr 2013;18:139-49.
- 13 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5 ed. Arlington, VA: American Psychiatric Publishing 2013.
- 14 Trivedi MH, Greer TL. *Cognitive dysfunction in unipolar depression: implications for treatment*. J Affect Disord 2014;152-4:19-27.
- 15 Airaksinen E, Wahlin A, Forsell Y, et al. *Low episodic memory performance as a premorbid marker of depression: evidence from a 3-year follow-up*. Acta Psychiatr Scand 2007;115:458-65.
- 16 Conradi HJ, Ormel J, de JP. *Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study*. Psychol Med 2010;8:1-10.
- 17 Potter GG, Kittinger JD, Wagner HR, et al. *Prefrontal neuropsychological predictors of treatment remission in late-life depression*. Neuropsychopharmacology 2004;29:2266-71.
- 18 McLennan SN, Mathias JL. *The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review*. Int J Geriatr Psychiatry 2010;25:933-44.
- 19 Mackin RS, Nelson JC, Delucchi K, et al. *Cognitive outcomes after psychotherapeutic interventions for major depression in older adults with executive dysfunction*. Am J Geriatr Psychiatry 2014;22:1496-503.
- 20 Pringle A, McCabe C, Cowen PJ, et al. *Antidepressant treatment and emotional processing: can we dissociate the roles of serotonin and noradrenaline?* J Psychopharmacol 2013;27:719-31.
- 21 Baune BT, Renger L. *Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression--a systematic review*. Psychiatry Res 2014;219:25-50.
- 22 McIntyre RS, Lophaven S, Olsen CK. *A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults*. Int J Neuropsychopharmacol 2014;17:1557-67.
- 23 Herrera-Guzmán I, Herrera-Abarca JE, Gudayol-Ferré E, et al. *Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on attention and executive functions in patients with major depressive disorder*. Psychiatry Res 2010;177:323-9.
- 24 Herzallah MM, Moustafa AA, Natsheh JY, et al. *Learning from negative feedback in patients with major depressive disorder is attenuated by SSRI antidepressants*. Front Integr Neurosci 2013;7:67.
- 25 Langenecker SA, Jacobs RH, Passarotti AM. *Current Neural and Behavioral Dimensional Constructs across Mood Disorders*. Curr Behav Neurosci Rep 2014;1:144-53.
- 26 Joormann J, Quinn ME. *Cognitive processes and emotion regulation in depression*. Depress Anxiety. 2014;31:308-15.
- 27 Hu T, Zhang D, Wang J, et al. *Relation between emotion regulation and mental health: a meta-analysis review*. Psychol Rep 2014;114:341-62.
- 28 Okon-Singer H, Hendler T, Pessoa L, et al. *The neurobiology of emotion-cognition interactions: fundamental ques-*

- tions and strategies for future research. *Front Hum Neurosci* 2015;9:58.
- ²⁹ Diener C, Kuehner C, Brusniak W, et al. *A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression*. *Neuroimage* 2012;61:677-85.
- ³⁰ Diamond A. *Executive functions*. *Annu Rev Psychol* 2013;64:135-68.
- ³¹ Alexopoulos GS, Meyers BS, Young RC, et al. *Executive dysfunction and long-term outcomes of geriatric depression*. *Arch Gen Psychiatry* 2000;57:285-90.
- ³² Majer M, Ising M, Künzel H, et al. *Impaired divided attention predicts delayed response and risk to relapse in subjects with depressive disorders*. *Psychol Med* 2004;34:1453-63.
- ³³ Castaneda AE, Suvisaari J, Marttunen M, et al. *Cognitive functioning in a population-based sample of young adults with a history of non-psychotic unipolar depressive disorders without psychiatric comorbidity*. *J Affect Disord* 2008;110:36-45.
- ³⁴ Herrera-Guzmán I, Gudayol-Ferré E, Lira-Mandujano J, et al. *Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder*. *Psychiatry Res* 2008;160:72-82.
- ³⁵ McDermott LM, Ebmeier KP. *A meta-analysis of depression severity and cognitive function*. *J Affect Disord* 2009;119:1-8.
- ³⁶ Hasselbalch BJ, Knorr U, Kessing LV. *Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review*. *J Affect Disord* 2011;134:20-31.
- ³⁷ Hermens DF, Redoblado Hodge MA, Naismith SL, et al. *Neuropsychological clustering highlights cognitive differences in young people presenting with depressive symptoms*. *J Int Neuropsychol Soc* 2011;17:267-76.
- ³⁸ Maalouf FT, Brent D, Clark L, et al. *Neurocognitive impairment in adolescent major depressive disorder: state vs. trait illness markers*. *J Affect Disord* 2011;133:625-32.
- ³⁹ Lee RS, Hermens DF, Porter MA, Redoblado-Hodge MA. *A meta-analysis of cognitive deficits in first-episode major depressive disorder*. *J Affect Disord* 2012;140:113-24.
- ⁴⁰ Wagner S, Doering B, Helmreich I, et al. *A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment*. *Acta Psychiatr Scand* 2012;125:281-92.
- ⁴¹ Baer LH, Tabri N, Blair M, et al. *Longitudinal associations of need for cognition, cognitive activity, and depressive symptomatology with cognitive function in recent retirees*. *J Gerontol B Psychol Sci Soc Sci* 2013;68:655-64.
- ⁴² Snyder HR. *Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review*. *Psychol Bull* 2013;139:81-132.
- ⁴³ Boelen PA, Huntjens RJ, van den Hout MA. *Concurrent and prospective associations of habitual overgeneral memory and prolepsis with symptoms of depression, general anxiety, obsessive compulsiveness, and post-traumatic stress*. *Memory* 2014;22:747-58.
- ⁴⁴ Li YR, Weinborn M, Loft S, et al. *Cognitive control processes underlying time-based prospective memory impairment in individuals with high depressive symptomatology*. *Acta Psychol (Amst)* 2014;149:18-23.
- ⁴⁵ Lin F, Suhr J, Diebold S, et al. *Associations between depressive symptoms and memory deficits vary as a function of insulin-like growth factor (IGF-1) levels in healthy older adults*. *Psychoneuroendocrinology* 2014;42:118-23.
- ⁴⁶ Pizzagalli DA. *Frontocingulate dysfunction in depression: toward biomarkers of treatment response*. *Neuropsychopharmacology* 2011;36:183-206.
- ⁴⁷ Etkin A, Gyurak A, O'Hara R. *A neurobiological approach to the cognitive deficits of psychiatric disorders*. *Dialogues Clin Neurosci* 2013;15:419-29.
- ⁴⁸ Palmer SM, Crewther SG, Carey LM, et al. *A meta-analysis of changes in brain activity in clinical depression*. *Front Hum Neurosci* 2015;8:1045.
- ⁴⁹ Sheline YI, Barch DM, Price JL, et al. *The default mode network and self-referential processes in depression*. *Proc Natl Acad Sci U S A*. 2009;106:1942-7.
- ⁵⁰ Walter M, Henning A, Grimm S, et al. *The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression*. *Arch Gen Psychiatry* 2009;66:478-86.
- ⁵¹ Hamilton JP, Furman DJ, Chang C, et al. *Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination*. *Biol Psychiatry* 2011;70:327-33.
- ⁵² Demeyer I, De Lissnyder E, Koster EH, et al. *Rumination mediates the relationship between impaired cognitive control for emotional information and depressive symptoms: a prospective study in remitted depressed adults*. *Behav Res Ther* 2012;50:292-7.
- ⁵³ Foland-Ross LC, Gotlib IH. *Cognitive and neural aspects of information processing in major depressive disorder: an integrative perspective*. *Front Psychol* 2012;3:489.
- ⁵⁴ Foland-Ross LC, Hamilton P, Sacchet MD, et al. *Activation of the medial prefrontal and posterior cingulate cortex during encoding of negative material predicts symptom worsening in major depression*. *Neuroreport* 2014;25:324-9.
- ⁵⁵ Miskowiak KW, Carvalho AF. *'Hot' cognition in major depressive disorder: a systematic review*. *CNS Neurol Disord Drug Targets* 2014;13:1787-803.
- ⁵⁶ Mackinger HF, Pachinger MM, Leibetseder MM, et al. *Autobiographical memories in women remitted from major depression*. *J Abnorm Psychol* 2000;109(2):331-4.
- ⁵⁷ Mogg K, Millar N, Bradley BP. *Biases in eye movements to threatening facial expressions in generalized anxiety disorder and depressive disorder*. *J Abnorm Psychol* 2000;109:695-704.
- ⁵⁸ Neshat-Doost HT, Moradi AR, Taghavi MR, et al. *Lack of attentional bias for emotional information in clinically depressed children and adolescents on the dot probe task*. *J Child Psychol Psychiatry* 2000;41:363-8.
- ⁵⁹ Dozois DJ, Dobson KS. *Information processing and cognitive organization in unipolar depression: specificity and comorbidity issues*. *J Abnorm Psychol* 2001;110:236-46.
- ⁶⁰ Murphy FC, Rubinsztein JS, Michael A, et al. *Decision-making cognition in mania and depression*. *Psychol Med* 2001;31:679-93.
- ⁶¹ Murphy FC, Michael A, Robbins TW, et al. *Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance*. *Psychol Med* 2003;33:455-67.
- ⁶² Bhagwagar Z, Cowen PJ, Goodwin GM, et al. *Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression*. *Am J Psychiatry* 2004;161:166-8.
- ⁶³ Gotlib IH, Krasnoperova E, Yue DN, et al. *Attentional biases for negative interpersonal stimuli in clinical depression*. *J Abnorm Psychol* 2004;113:121-35.
- ⁶⁴ Joormann J, Siemer M. *Memory accessibility, mood regulation, and dysphoria: difficulties in repairing sad mood with happy memories?* *J Abnorm Psychol* 2004;113:179-88.
- ⁶⁵ Leppanen JM, Milders M, Bell JS, et al. *Depression biases the recognition of emotionally neutral faces*. *Psychiatry Res* 2004;128:123-33.

- ⁶⁶ Hayward G, Goodwin GM, Cowen PJ, et al. *Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms*. *Biol Psychiatry* 2005;57:517-24.
- ⁶⁷ Raes F, Hermans D, Williams JM, et al. *Reduced specificity of autobiographical memory: a mediator between rumination and ineffective social problem-solving in major depression?* *J Affect Disord* 2005;87(2-3):331-5.
- ⁶⁸ Joormann J, Gotlib IH. *Selective attention to emotional faces following recovery from depression*. *J Abnorm Psychol* 2007;116:80-5.
- ⁶⁹ Joormann J, Siemer M, Gotlib IH. *Mood regulation in depression: Differential effects of distraction and recall of happy memories on sad mood*. *J Abnorm Psychol* 2007;116:484-90.
- ⁷⁰ Gollan JK, Pane HT, McCloskey MS, et al. *Identifying differences in biased affective information processing in major depression*. *Psychiatry Res* 2008;159:18-24.
- ⁷¹ Harmer CJ, O'Sullivan U, Favaron E, et al. *Effect of acute antidepressant administration on negative affective bias in depressed patients*. *Am J Psychiatry* 2009;166:1178-84.
- ⁷² LeMoult J, Joormann J, Sherdell L, et al. *Identification of emotional facial expressions following recovery from depression*. *J Abnorm Psychol* 2009;118:828-33.
- ⁷³ Chase HW, Frank MJ, Michael A, et al. *Approach and avoidance learning in patients with major depression and healthy controls: relation to anhedonia*. *Psychol Med* 2010;40:433-40.
- ⁷⁴ Milders M, Bell S, Platt J, et al. *Stable expression recognition abnormalities in unipolar depression*. *Psychiatry Res* 2010;179:38-42.
- ⁷⁵ Anderson IM, Shippen C, Juhasz G, et al. *State-dependent alteration in face emotion recognition in depression*. *Br J Psychiatry* 2011;198:302-8.
- ⁷⁶ Sterzer P, Hilgenfeldt T, Freudenberg P, et al. *Access of emotional information to visual awareness in patients with major depressive disorder*. *Psychol Med* 2011;41:1615-24.
- ⁷⁷ Atchley RA, Ilardi SS, Young KM, et al. *Depression reduces perceptual sensitivity for positive words and pictures*. *Cogn Emot* 2012;26:1359-70.
- ⁷⁸ Hu Z, Liu H, Weng X, et al. *Is there a valence-specific pattern in emotional conflict in major depressive disorder? An exploratory psychological study*. *PLoS One* 2012;7:e31983.
- ⁷⁹ Kunisato Y, Okamoto Y, Ueda K, et al. *Effects of depression on reward-based decision making and variability of action in probabilistic learning*. *J Behav Ther Exp Psychiatry* 2012;43:1088-94.
- ⁸⁰ Treadway MT, Bossaller NA, Shelton RC, et al. *Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia*. *J Abnorm Psychol* 2012;121:553-8.
- ⁸¹ Everaert J, Tierens M, Uzieblo K, et al. *The indirect effect of attention bias on memory via interpretation bias: evidence for the combined cognitive bias hypothesis in subclinical depression*. *Cogn Emot* 2013;27:1450-9.
- ⁸² Kruijt AW, Antypa N, Booij L, et al. *Cognitive reactivity, implicit associations, and the incidence of depression: a two-year prospective study*. *PLoS One* 2013;8:e70245.
- ⁸³ Romero N, Sanchez A, Vazquez C. *Memory biases in remitted depression: the role of negative cognitions at explicit and automatic processing levels*. *J Behav Ther Exp Psychiatry* 2014;45:128-35.
- ⁸⁴ Schroder HS, Moran TP, Infantolino ZP, et al. *The relationship between depressive symptoms and error monitoring during response switching*. *Cogn Affect Behav Neurosci* 2013;13:790-802.
- ⁸⁵ Orgeta V. *Emotion recognition ability and mild depressive symptoms in late adulthood*. *Exp Aging Res* 2014;40:1-12.
- ⁸⁶ Takano K, Iijima Y, Sakamoto S, et al. *Exploring the cognitive load of negative thinking: a novel dual-task experiment*. *J Behav Ther Exp Psychiatry* 2014;45:435-40.
- ⁸⁷ Vanderlind WM, Beevers CG, Sherman SM, et al. *Sleep and sadness: exploring the relation among sleep, cognitive control, and depressive symptoms in young adults*. *Sleep Med* 2014;15:144-9.
- ⁸⁸ Yoon KL, LeMoult J, Joormann J. *Updating emotional content in working memory: a depression-specific deficit?* *J Behav Ther Exp Psychiatry* 2014;45:368-74.
- ⁸⁹ Pfeiffer N, Brockmeyer T, Zimmermann J, et al. *The temporal dynamics of cognitive reactivity and their association with the depression risk: an exploratory study*. *Psychopathology* 2015;48:114-9.
- ⁹⁰ Remmers C, Topolinski S, Dietrich DE, et al. *Impaired intuition in patients with major depressive disorder*. *Br J Clin Psychol* 2015;54:200-13.
- ⁹¹ Everaert J, Duyck W, Koster EH. *Attention, interpretation, and memory biases in subclinical depression: a proof-of-principle test of the combined cognitive biases hypothesis*. *Emotion* 2014;14:331-40.
- ⁹² Gotlib IH, Joormann J. *Cognition and depression: current status and future directions*. *Annu Rev Clin Psychol* 2010;6:285-312.
- ⁹³ Joormann J, Gotlib IH. *Is this happiness I see? Biases in the identification of emotional facial expressions in depression and social phobia*. *J Abnorm Psychol* 2006;115:705-14.
- ⁹⁴ Weightman MJ, Air TM, Baune BT. *A review of the role of social cognition in major depressive disorder*. *Front Psychiatry* 2014;5:179.
- ⁹⁵ Kerestes R, Ladouceur CD, Meda S, et al. *Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters*. *Psychol Med* 2012;42:29-40.
- ⁹⁶ Wang Y, Zhou Y, Li S, et al. *Impaired social decision making in patients with major depressive disorder*. *BMC Psychiatry* 2014;14:18.
- ⁹⁷ Everaert J, Koster EH, Derakshan N. *The combined cognitive bias hypothesis in depression*. *Clin Psychol Rev* 2012;32:413-24.
- ⁹⁸ Eshel N, Roiser JP. *Reward and punishment processing in depression*. *Biol Psychiatry* 2010;68:118-24.
- ⁹⁹ Elliott R, Sahakian BJ, McKay AP, et al. *Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance*. *Psychol Med* 1996;26:975-89.
- ¹⁰⁰ Henriques JB, Glowacki JM, Davidson RJ. *Reward fails to alter response bias in depression*. *J Abnorm Psychol* 1994;103:460-6.
- ¹⁰¹ Kasch KL, Rottenberg J, Arnow BA, et al. *Behavioral activation and inhibition systems and the severity and course of depression*. *J Abnorm Psychol* 2002;111:589-97.
- ¹⁰² Kerestes R, Davey CG, Stephanou K, et al. *Functional brain imaging studies of youth depression: a systematic review*. *Neuroimage Clin* 2013;4:209-31.
- ¹⁰³ Wang L, LaBar KS, Smoski M, et al. *Prefrontal mechanisms for executive control over emotional distraction are altered in major depression*. *Psychiatry Res* 2008;163:143-55.
- ¹⁰⁴ Dichter GS, Felder JN, Smoski MJ. *Affective context interferes with cognitive control in unipolar depression: an fMRI investigation*. *J Affect Disord* 2009;114:131-42.
- ¹⁰⁵ Roberson-Nay R, McClure EB, Monk CS, et al. *Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: An FMRI study*. *Biol Psychiatry* 2006;60:966-73.

- ¹⁰⁶ Hamilton JP, Gotlib IH. *Neural substrates of increased memory sensitivity for negative stimuli in major depression*. *Biol Psychiatry* 2008;63:1155-62.
- ¹⁰⁷ Stuhmann A, Suslow T, Dannlowski U. *Facial emotion processing in major depression: a systematic review of neuroimaging findings*. *Biol Mood Anxiety Disord* 2011;1:10.
- ¹⁰⁸ Sheline YI, Barch DM, Donnelly JM, et al. *Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study*. *Biol Psychiatry* 2001;50:651-8.
- ¹⁰⁹ Victor TA, Furey ML, Fromm SJ, et al. *The extended functional neuroanatomy of emotional processing biases for masked faces in major depressive disorder*. *PLoS One* 2012;7:e46439.
- ¹¹⁰ Davey CG, Allen NB, Harrison BJ, et al. *Increased amygdala response to positive social feedback in young people with major depressive disorder*. *Biol Psychiatry* 2011;69:734-41.
- ¹¹¹ Olino TM, McMakin DL, Dahl RE, et al. *"I won, but I'm not getting my hopes up": depression moderates the relationship of outcomes and reward anticipation*. *Psychiatry Res* 2011;194:393-5.
- ¹¹² Pizzagalli DA, Holmes AJ, Dillon DG, et al. *Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder*. *Am J Psychiatry* 2009;166:702-10.
- ¹¹³ Smoski MJ, Felder J, Bizzell J, et al. *fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder*. *J Affect Disord* 2009;118:69-78.
- ¹¹⁴ Stoy M, Schlagenhaut F, Sterzer P, et al. *Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram*. *J Psychopharmacol* 2012;26:677-88.
- ¹¹⁵ Grimm S, Boesiger P, Beck J, et al. *Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects*. *Neuropsychopharmacology* 2009;34:932-43.
- ¹¹⁶ Gualtieri CT, Morgan DW. *The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials*. *J Clin Psychiatry* 2008;69:1122-30.
- ¹¹⁷ Gorwood P, Corruble E, Falissard B, et al. *Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients*. *Am J Psychiatry* 2008;165:731-9.
- ¹¹⁸ Preiss M, Kucerova H, Lukavsky J, et al. *Cognitive deficits in the euthymic phase of unipolar depression*. *Psychiatry Res* 2009;169:235-9.
- ¹¹⁹ Vanderhasselt MA, De Raedt R, Dillon DG, et al. *Decreased cognitive control in response to negative information in patients with remitted depression: an event-related potential study*. *J Psychiatry Neurosci* 2012;37:250-8.
- ¹²⁰ Hakamata Y, Matsui M, Tagaya H. *Does neurocognitive function affect cognitive bias toward an emotional stimulus? Association between general attentional ability and attentional bias toward threat*. *Front Psychol* 2014;5:881.
- ¹²¹ Johnstone T, van Reekum CM, Urry HL, et al. *Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression*. *J Neurosci* 2007;27:8877-84.
- ¹²² Erk S, Mikschl A, Stier S, et al. *Acute and sustained effects of cognitive emotion regulation in major depression*. *J Neurosci* 2010;30:15726-34.
- ¹²³ Kanske P, Heissler J, Schonfelder S, et al. *Neural correlates of emotion regulation deficits in remitted depression: the influence of regulation strategy, habitual regulation use, and emotional valence*. *Neuroimage* 2012;61:686-93.
- ¹²⁴ Greening SG, Osuch EA, Williamson PC, et al. *The neural correlates of regulating positive and negative emotions in medication-free major depression*. *Soc Cogn Affect Neurosci* 2014;9:628-37.
- ¹²⁵ Smoski MJ, Keng SL, Schiller CE, et al. *Neural mechanisms of cognitive reappraisal in remitted major depressive disorder*. *J Affect Disord* 2013;151:171-7.
- ¹²⁶ Beck AT. *Cognitive therapy and emotional disorders*. New York: International University Press 1976.
- ¹²⁷ Roiser JP, Elliott R, Sahakian BJ. *Cognitive mechanisms of treatment in depression*. *Neuropsychopharmacology* 2012;37:117-36.
- ¹²⁸ Harmer CJ, Goodwin GM, Cowen PJ. *Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action*. *Br J Psychiatry* 2009;195:102-8.
- ¹²⁹ Johnco C, Wuthrich VM, Rapee RM. *The influence of cognitive flexibility on treatment outcome and cognitive restructuring skill acquisition during cognitive behavioural treatment for anxiety and depression in older adults: Results of a pilot study*. *Behav Res Ther* 2014;57:55-64.