Chapter from the book *Major Depressive Disorder - Cognitive and Neurobiological Mechanisms*

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1. Introduction

Depression is one of the most prevalent mood disorders worldwide which threatens human mental health and well-being. Major depressive disorder is characterized by excessive negative mood and reduced experience of pleasure (anhedonia). The etiology of depression is much too complicated to explain when a wide spectrum of cognitive, affective, neurobiological symptoms taken into consideration.

According to Beck’s influential cognitive theory, depression is characterized by presence of negative schemas, defined as mental representations of past experiences, containing dysfunctional attitudes about the self. These underlying schemas have an important influence on the way information is processed, guiding one’s attention, memory and interpretation for personally relevant negative experiences [1]. Recent studies have proved that the negative schema can produce cognitive deficits such as negative attentional bias, over general autobiographical memory, cognitive control deficits. These cognitive deficits make people with depression inclined to choose negative material consistent with their negative schema, which cause persistent and recurrent depressive episodes. Other researchers used a variant of behavior paradigms, and neuroscience techniques such as Event-Related Potential (ERP) and Functional Magnetic Resonance Imaging (fMRI) to delineate the negative attentional bias, emotion dysregulation, over-general autobiographical memory, cognitive control deficits underpinning depression. However, several important questions remain. How do people with depression develop cognitive deficits? Can cognitive deficits predict the onset and process of depression? Can we fix the cognitive deficits of depressed individuals? What are the neural substrates underlying these cognitive deficits? If we can answer these questions, depression...
Attention is the first step of cognitive process, but what role does it play in the negative cognitive bias? There is a large and growing literature trying to determine the cognitive mechanism that may underlie such attentional inflexibility in depressed individuals. Recent studies have found that people with depression are inclined to avoid positive stimuli while difficult to disengage attention from negative stimuli in dot probe detection task [2]. Similarly, people with depression cannot rule out the impact of emotion on the performance, their reaction time (RT) is prolonged when they are faced with sad faces [3]. Besides, studies using ERP have shown that when people with depression are presented with sad faces, their P3 will be delayed and stronger which means that dysphoric people pay more attention to negative stimulus [4], reflecting more elaborate processing of negative stimuli. These results indicate that people with depression have negative attentional bias which make people with depressive symptoms tend to focus on the negative stimulus, which consequently lead to sustained and exacerbated symptoms of depression.

Emotion appraisal and regulation are two essential systems underpinning the process of emotional cognition. It is widely assumed that the initial appraisals of emotion events are the starting point for iterative cycles of appraising and reappraising that extend beyond the events themselves. Thus the initial appraisals must play an essential role in the negative bias of depression. Emotional appraisal is described as a multidimensional neural processing including sensory inputs and affective experience. To be noted, Emotion Context Insensitivity Hypothesis proposes that major depression is characterized by flattened emotional reactivity to both positive and negative valenced stimuli, with the reduction greater for positive stimuli [5]. Thus the positive and negative emotion system might be two relatively independent and interacting processes that need further exploration.

Autobiographical memory is a memory system consisting of episodes recollected from an individual’s life, consisting of both episodic and semantic memory. Over general autobiographical memory is a key symptom of depression which is sustained over episodes of depression. Longitudinal studies focused on currently depressed patients and high-risk population found that the more over general autobiographical memory is, the longer depression is sustained. As a result, some researchers proposed that over general autobiographical memory play an essential role in the etiology of depression. Large amounts of researches have been done to delineate healthy people’s autobiographical memory. Recent studied using behavioral methods have shown that the inhibition of other unrelated memory play an important role in the construction of autobiographical memory. Besides, studies using fMRI have discovered related brain circuits underpinning autobiographical memory [6]. Although much work has been done, some questions still remain: how does the depressive brain activate when it try to recall an autobiographical memory? You can read the attempts to find the answers in the following part of this chapter.

Disturbed interface between cognitive control and emotion processing. Recent research has suggested that impairments in memory and attention are related to cognitive control deficits. Consequently, persistent sad mood may be maintained by negative attentional bias. Mean-
while, anhedonia or flattened emotion pattern may be linked with abnormal processing of positive stimuli. Thus the cause of depression may be linked with altered emotional processing or impaired cognitive control. It remained largely unknown whether emotional processing and cognitive control affect the negative cognitive bias independently or reciprocally. Researches in this area have suggested that the negative cognitive bias reflect the over activated bottom-up system, which is related to over activated amygdala, fusiform gyrus and enlarged early P300 in ERP studies. Meanwhile, other researchers indicated that top-down cognitive control deficit can explain depression’s negative cognitive bias. This deficit is associated with the hypo-activated dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulated cortex (dACC), rostral anterior cingulated cortex (rACC) and the smaller N450 and N200 in ERP studies [7]. Most researches explain negative cognitive bias either from down-top prospect (amygdala, fusiform gyrus) or from top-down perspective (e.g. DLPFC, dACC). But results of some studies indicate that these two system work together to form the negative cognitive bias. When negative information is processed by people with depression, bottom-up system may be over activated (e.g. over activated amygdala), while the weakened inhibition function of the top-down system may exacerbate this process and form a maladaptive circle which may lead to a depressive episode finally.

Although much effort has been made to uncover the mystery of depression, many questions about the depression’s neural basis still remain. Firstly, we cannot find a valuable predictor to the depressive episode’s onset yet. Secondly, the association between negative cognitive bias and the specific brain deficits (neural circuit) is not yet quite clear. Not until recently, we just began to understand the neural process underlying the cognitive training and rTMS directed to depression. Though these questions seem difficult to answer, they may be the key for us to conquer depression in the future.

2. The neurocognitive mechanisms behind attentional bias in depression

According to Beck’s theory, individuals’ existing memory representations, or schemas, made their attention directed to the information that is congruent with their own schemas, and initiated a vicious cycle of negative automatic thoughts, processing biases, and depressed mood [8]. Moreover, differential attentional bias to negative information has been considered a cognitive vulnerability factor for the development of depression [9]. For this reason, attentional bias have drawn researchers’ attention and been supported by various studies.

2.1. Theories on attentional bias in depression and limitations

Attentional bias could be understood from the perspectives of attention process, narrow focus of attention, cognitive load and arousal level [10].

Attention processes include orienting, maintenance and disengagement, and it is still controversial to say which progress leads to attentional bias. For one explanation, attention may be attracted to or directed away from the position of negative stimuli in the orienting progress [11]. For another, it is the attention disengagement that emotional stimuli affects, making
maintained attention to the negative stimuli, or being relatively easier distracted from positive
stimuli [9]. It is significant to discuss from a dynamic point of view, but it has its own limitation
for further study on specific mechanism.

**Theories on narrow focus of attention** refers to that depressed patients may selectively attend
to depression-related information and process mood-congruent material easier, while ignoring
other information, which represents attention bias. This interpretation represents neural
network specificity while ignores the control ability of neural pathways for information
processing [12].

When it comes to **cognitive capacity theory**, some postulate that individuals can only perform
limited mental activity due to fixed amount of cognitive resource. When negative stimuli
appear with other stimuli, depressed individuals’ attentional resource can easily be occupied
with the negative one, leaving little cognitive resources to other tasks and making them
uncompleted. Other experts then believe depressed ones are more engaged in their internal
mental activity, while they are less sensitive to external stimuli. Sometimes they only respond
to intense stimuli. This can be well explained by **parallel distributed processing (PDP) model** [13].
Research showed that stimulus which was either too weak or not associated with depression
was not reach the arousal level of subjects and therefore no attentional bias was observed [14].

Here come limitations with these existing explanations. Firstly, it is unclear that which
mechanism, facilitation or inhibition, leads to attentional bias. Selective attention means
processing information selectively which lead to activation for relevant information and
inhibition for irrelevant or interferential information. Or maybe the cooperation of two
mechanisms makes selective attention. Secondly, what is the relationship between attentional
bias and depression? It is attentional bias that cause depression or just in reverse. Or maybe
attentional bias is just one of cognitive features of depression.

2.2. Researches on attentional bias

To further understand these questions, we need firstly get a picture of research paradigms in
this field as well as the features of attentional bias in depressed patients.

2.2.1. Research paradigms for attentional bias

Stroop task, or emotionally modified stroop task, is the principal paradigm for attentional bias.
By measuring subjects’ reaction time performance in color-naming task or emotional words
and its accuracy, interference inhibition is appraised indirectly.

Dot-probe detection task help demonstrate orienting or maintenance of attention. If subject
had a shorter reaction time for target stimulus presented following a negative stimulus, he
may have the attentional bias for negative stimuli.

Cue-target paradigm can observe orienting and disengagement of attention (Fig. 1). With
emotional stimuli being valid and invalid cues, if subjects have shorter reaction time to
negative valid stimuli and longer reaction time to negative invalid stimuli, they may present
attentional bias.
Garner paradigm is mainly used to investigate the maintenance of attention by studying the interaction of two variables, while the negative priming paradigms discuss attentional bias mainly from the angle of distracter inhibition. The latter task is designed to distinguish activation from inhibition which accounts of selective attention. The negative priming effect is defined as longer response latency when the distracter from a previous trial becomes the target on the present trial. And the distractor that activates in two trials may cause a delay response.

2.2.2. Features of attentional bias in depressed patients

Results of previous studies on the attentional bias of depression have been mixed, and the inconsistencies have been ascribed to differences among subjects, stimulus exposure duration, content and intensity. Therefore, features of attentional bias in depressed patients should be mentioned. Firstly, attentional bias to negative stimuli was found significant in researches with study subjects being clinical depressed patients. But when it comes to college students whose depression scores are relative high, biased processing of negative information is not significant [15]. Therefore, it is only when individuals get severe depression may significant attentional bias occur. Secondly, attentional bias occurs only when the stimuli last longer than the time threshold. In general, 1000ms is considered the best choice. For depressed patients, the internal attentional bias may lower their external stimuli arouse level and make it difficult to response to the stimuli from outside. Thus stimuli have been presented long enough for depressed individuals to aware and process. This has been shown in Bradley’s and Gotlib’s experiments. The former reported a mood-congruent bias on the dot-probe task under conditions of long stimuli exposures of 500 or 1000ms, but not under conditions of brief durations [16]. The latter had stimuli presented for 1000ms and observed attentional bias for negative faces in clinically diagnosed depressed patients [17]. Thirdly, the content of stimuli should be specific to depressed patients. Study with stimuli relevant to anxiety or self–esteem threat did not show attentional bias[18], but studies on sad faces or depression relevant words could induce
negative attentional bias[11, 19]. The emotion-congruent information may strike a responsive chord in the heart of subjects who will show specific attentional bias for these negative stimuli. Fourthly, too weak stimulus intensity should be avoided. Emotional words, emotional faces, and emotional pictures are three types of stimuli that are widely used nowadays. Because emotional words always need deeper cognitive processing and emotional faces interpret more social information, these two types stimuli can induce more intense emotional experience. That is the reason why they are popular used. It seems that participants diagnosed with a current major depressive disorder (MDD) show attentional bias for long-exposed and very intense stimuli.

2.3. Cognitive neuroscience basis of attentional bias

In normal individuals, the anterior cingulate regulates the attention–emotion balance by signaling to the dorsolateral prefrontal cortex [20]. However, depressed individuals show less activation in these regions [21], which might relate to their inability to gain attentional control over emotional interference. Moreover, evidence showed that depressed subjects were more easily distracted by negative information, and spent significantly more time on processing these negative stimuli [22, 23]. Therefore, attentional control for emotional stimuli in depressed patients, especially deficient inhibition for attention to negative stimuli, needs further exploration.

Three kinds of attentional inhibitions have been explored: inhibition of return (IOR), distracter inhibition and interference inhibition.

IOR means a slower response to objects appearing at a formerly-attended location, which typically appears about 200–300 ms after stimulus offset. We investigated this phenomenon in depressed individuals with a cue target paradigm as emotional faces being cues in an event-related potential (ERP) experiment. Three groups of participants were recruited representing the health control (NC), the remitted depressive patients (RMD), and the major depressive disorder (MDD) group respectively. The MDD participants were found to have cue validity and deficient IOR for negative stimuli. The deficient inhibition of negative stimuli renders them unable to eliminate the interference of negative stimuli and causes the maintenance and development of depression [24].

To investigate distracter inhibition and facilitation for emotional faces in depressed individuals, we used a modified negative priming paradigm-Negative Affective Priming task (NAP) among three groups of subjects (NC, RMD and MDD). Though there were no significant differences among the three groups in the positive and negative priming effects of happy faces, differences between each pair of groups are significant for sad faces. Depressed individuals are found characterized by enhanced facilitation and deficient inhibition for negative materials, which is a stable cognitive vulnerability factor and is probably associated with occurrence of depression [25, 26].

Interference inhibition was investigated in current remitted depression using the emotional Stroop task and the event-related potential (ERP) technique. MDD participants had higher interference effects for negative words compared with the other two groups and those of
positive stimuli. With regard to the ERP data, the MDD participants showed smaller N1 amplitude for negative words and a smaller P1 amplitude for positive words in bilateral hemispheres compared with the other groups. Both the MDD and RMD participants showed enhanced negativity (N450) over the parietal regions of the brain for negative words compared with NC groups [27].

In conclusion, negative attentional bias, an important contributor to the maintenance and development of depression, correlates with susceptibility to depression. The clinical psychologist could pay more attention on the training of intentional inhibition of negative stimuli during clinical intervention. These findings also provide a theoretical foundation for cognitive therapy, that is to say, patients can be cured by leading them to neglect or inhibit negative stimuli, or to pay more attention to positive ones. However, the correlation between attentional bias and depression remains unsolved. If attentional bias is causal, it is difficult to explain it in RMD participants.

3. Emotion appraisal and regulation disorder in depression

Emotion dysregulation is characteristic of MDD which occurred during an emotion generating episode. While emotion reactivity and regulation are two sides of a coin, emotion regulation is always explicitly or implicitly existent in emotion responses. Thus the need to change the initial negatively biased emotion responses is in particular essential for depressed patients.

3.1. Abnormal emotion reactivity

Loss of interest or pleasure is the core feature of depression, which may be manifested as lingering low mood and a reduced capacity to experience pleasure. Cognitive theories put maladaptive appraisal processes at the core of depression [28]. According to Gross’ s model of emotion, the initial appraisals of emotion events are frequently the starting point for iterative cycles of appraising and reappraising that extend beyond the events themselves[29]. Thus the need to change the initial negatively biased emotion responses is in particular essential for depressed patients.

 Emotional appraisal has been presumed to span a hierarchy of neural processing, from sensory inputs to affective experience. Depression-related disruption of this hierarchical processing system may extending from sensory to frontal regions through insula [30]. Researchers have proposes Emotion Context Insensitivity (ECI) hypothesis that major depression is characterized by flattened emotional reactivity to both positive and negative valenced stimuli, with the reduction greater for positive stimuli[31]. And ECI was supported in three main subsystems of emotion response: peripheral physiology, expressive behavior and self-reported arousal [32]. At resting state, amygdala-hippocampal/brainstem and amygdala-precuneus may be circuits that are important for modulation of physiologic responses to emotion which are impaired and contribute to both mood and vegetative symptoms [33]. During the completion of emotional intensity evaluation, we found that more excited perception for negative facial expressions is a stable cognitive vulnerability possibly associated with the occurrence or
recurrence of depression [34]. This could partly explain a generalized emotional hypoactivity in major depression.

3.2. Disrupted emotion regulation

While emotion reactivity and regulation are two sides of a coin, emotion regulation is always explicitly or implicitly existent in emotion responses. Emerging evidence emphasizes the role of emotion regulation capacity in the neurological model of depression; depressed patients exhibit difficulties implementing adaptive emotion regulation strategies and more frequent use maladaptive strategies. However, the mechanisms underlying the difficulties in emotion regulation remain unclear.

A long tradition of cognitive theory focused on a negative bias which causes the vulnerability and maintenance of major depression. Along with this tradition, Joormann et al proposes that cognitive biases and deficits in cognitive control typical of depression influence emotion regulation in critical ways, therefore resulting in maintained negative affect and diminished levels of positive affect[35]. The evidence was that difficulties with cognitive flexibility and control may impair performance on tasks that require processing of relevant emotional stimuli[36]. Neurally, depression may impair the cognitive capacity of depressed patients by recruiting more brain resources than controls during cognitive control. Accordingly, neuroimaging studies indicated increased activity within subcortical and ventral prefrontal cortical regions to negative emotional stimuli and decreased activity within dorsal prefrontal cortical regions in MDD patients.

Seminowicz et al put forward a limbic – cortical dysregulation model which proposes that sadness and depressive illness are both associated with decreases in dorsal neocortical regions (sensory-cognitive compartment) and relative increases in ventral limbic and paralimbic areas (autonomic compartment), and illness remission occurs when there is appropriate modulation of dysfunctional limbic–cortical interactions[37].

Phillips and colleagues schematize the neural basis of emotion perception and regulation deficits for major depression with a dorsal-ventral interaction model. Volume reductions within the amygdala and other components of the ventral neural system, together with increased activity within these regions during illness, may result in flattened emotional response patterns, biased toward the biased perception of negative emotions for amygdala [38]. The negative affectivity bias of depression can be seen during completion of emotional intensity evaluation task; we found that more excited perception for negative facial expressions is a stable cognitive vulnerability possibly associated with the occurrence or recurrence of depression [39]. Notably, negative bias might also been seen in bipolar depression, suggesting different pathophysiology processes for BD versus MDD depression. There was evidence that abnormally elevated left amygdala activity to mild sad and neutral faces might be a depression-specific marker in BD but not MDD, [40]. Thus further exploration into emotion processing disruption and neural mechanisms for MDD is necessary.

Structural and functional impairments within regions of the dorsal system, associated with impairments in executive function and effortful regulation of emotional behavior, may
perpetuate these phenomena, setting stage for lingering depressed mood and anhedonia. As an example, reappraisal ability of emotion stimuli is found to be impaired in depressed individuals. Patients seemed to have deficits in prefrontal-amygdala modulatory network during both up-regulation and down-regulation of emotion [41]. Other studies suggest that overregulation of the amygdala by the ventromedial prefrontal cortex/orbitomedial prefrontal cortex may lead to diminished amygdala responsiveness to happy faces in unipolar depressed patients [40, 42]. This could partly explain a generalized emotional hypoactivity in major depression.

3.2.1. Typical use of emotion regulation strategies

In the last decade, researchers have focused on the habitual use of specific strategies, examining the relation between use of adaptive and maladaptive strategies and psychopathology [43]. This line of research provides evidence that depressed individuals show a more dysfunctional use of emotion regulation strategies than controls. Maladaptive strategies (rumination, suppression), compared to adaptive strategies (reappraisal, problem-solving), were more strongly associated with depressive symptoms [44]. Across both male and female groups, higher reports of self-blame, rumination and/or catastrophizing as strategies were strongly related to higher depression scores, whereas higher reports of positive reappraisal were related to lower depression scores [45]. Moreover, these deficits are not limited to the acute phase but are also a risk factor for the development of recurrent depressive episodes [46]. MDD patients reported increased suppression of both negative and positive emotions. Suppression of negative and positive emotions was related to depressive symptoms. Results demonstrated that suppression produced short-term reductions in sadness, while for moderate and higher levels of anxiety about the experience of depressed mood suppression was no longer effective [47]. The explanation for why MDD patients suppress emotions might be the fear of strong emotion [48].

Past research has also paid attention to potential cultural and gender differences in emotion regulation [49]. For instance, the association between the use of reappraisal and depressive symptoms was significantly stronger in the Korean compared to the US sample. In contrast, the association between anger suppression and depressive symptoms was significantly stronger in the American compared to the Korean sample [50]. Due to these factors leading to individual differences of ER, examining individual differences in the habitual use of emotion-regulation strategies may have remarkable potential to clarify emotion regulation (ER) models of MDDs [35]. Recent findings suggest that individual differences in the use of emotion-regulation strategies play an important role in depression, and that deficits in cognitive control are associated with the use of maladaptive emotion-regulation strategies in this disorder.

3.2.2. Experimental manipulated emotion regulation

Some researchers study emotion regulation by instructing participants to engage in particular emotion-regulation strategy in response to an emotion eliciting stimulus and then observing the effects on participants’ subsequent emotions, cognitions, or physiological responding. Most of these studies have been conducted on the implementation of adaptive strategies, and
this area clearly should be a focus of future research on ER in this disorder [43]. Reappraisal is an adaptive emotion regulation strategy which involves the utilization of cognitive control to regulate semantic representations of affective stimuli. Findings are mixed when it comes to the question whether depressed people differ from their no depressed counterparts in their ability to reappraise. We inspect the role of self-perspective in reappraisal process of depressed patients in terms of goals (valence/arousal) and tactics (detachment/immersion). The results were that impaired modulatory effects of amygdala in depressed patients are compensated with strengthening cognitive control resources, with dissociable effects for different self-perspectives in reappraisal. This may help clarify the role of self-perspective underlying reappraisal in major depression [41]. We also found that depressed patients but not healthy controls enhanced their positive emotions while recruiting behavioral activation system (drive) underlying bilateral DLPFC. This may suggest a lack of control resources during generating positive emotion for depressed individuals, who are consequently more dependent on compensatory recruitment of control areas. Thus amplification of positive affect could be more difficult for depressed patients. These results fits nicely with the previously mentioned findings by Werner-Seidler et al. (2013) and Beblo et al. (2012) that depression is associated with fear of emotion and apprehension about experiencing intense emotion [51, 52].

3.2.3. Dispositional/spontaneous emotion regulation

Depression-vulnerable individuals might also be expected to abnormal in their spontaneous use of particular forms of emotion regulation when depressed [53]. Habitual styles of emotion regulation may determine the automatic regulation pathway suggested by Phillips et al. (2008) [54]. Conversely, there was also evidence that unconscious emotion-regulation processes may interplay with conscious emotion-regulation processes to affect mental health [55]. The paradigm of conscious emotion regulation was also problematic because participants may have underreported or inaccurately recalled their application of regulation strategies. Ehring et al proposed that spontaneous but not instructed emotion regulation play a more critical role in depression vulnerability [53]. Thus it would be necessary to examine the relationships between emotion-regulation strategies and psychopathology simultaneously at the dispositional and state level.

3.3. Emotion regulation: associations with affective style

It was reported that affective style reflecting approach and inhibition might interact with ER strategies to influence depressed mood [56]. Some researchers have suggested that depression is associated with a reduced sensitivity to reward and an increased sensitivity to punishment [57]. Moreover, to reappraise stimuli as appetitive/aversive is inherent in cognitive control process of emotion according to Gross’s model of cognitive control of emotion (MCCE) [58]. Our results revealed that an altered motivational pattern of BAS hypoactivity and BIS hyperactivity [59] with overlapping prefrontal circuits with reappraisal, would differentially affected the neural responses underlying reappraisal. And BIS/BAS measures were associated with prefrontal/amygdala activation during immersion but not detachment. Consequently,
high self-focused cognitive and ruminative tendency (particularly negative) for emotion regulation of depressed patients was implied.

To examine the abnormal resting state functional connectivity in major depression, fALFF were compared between groups using REST and further correlated with BIS/BAS in SPSS18.0. In controls, fALFF of right cerebellum was negatively correlated with BIS, fALFF of left medial frontal gyrus were negatively correlated with BASD. In MDD, fALFF of left median frontal gyrus was positively correlated with BASF. Conclusions The abnormal fALFF pattern of MDD was identified in default mode network and mood regulation circuit, and correlated with BIS/BAS index [60].

To conclude, there has been a long tradition of treatment for depression targeting emotion regulation malfunction. Different types of psychotherapy modulate aberrant emotion by engaging different but interacting pathways for emotion regulation. One promising therapy of Neurofeedback is attractive that it enables the patients themselves to voluntarily control their brain activity which increases their self-efficacy, which is an important therapeutic factor in many neuropsychiatric disorders [61]. During real-time fMRI-NF (Neurofeedback) training, participants receive feedback on their brain activity in real-time and are instructed to change this activation by instruction or imagery.

4. Over-generalization of autobiographical memory in depression

4.1. What is over-generalization of autobiographical memory?

Are you often absorbed in your happy reminiscences, such as your first date scene, or some bad moments like the day you lost your beloved dog? The specific reminiscences of past events you ever experienced or even more conceptual, self-related information are all called autobiographical memory [62].

You may have realized that autobiographical memory is just like a great album keeping our own moments important or not, some of which may influence us forever. Autobiographical memory is critical to the human experience, the influence of which mainly embodies in three aspects. First, it plays a key role in creating a sense of self and identity. Individuals could switch to their past times from the current time in the subject time dimension. Second, autobiographical memories serve as important guides for the future. As records of personal past experiences, such memories provide reminders of the lessons learned from them, thereby helping themselves or others to solve similar problems in the present or to plan for future action [63]. Third, it could help to reinforce social connection. For example, unfamiliar people can create trust and closeness with each other quickly by sharing similar life experiences.

Since Williams and Broadbent first described the overgeneral autobiographical memory (OGM) phenomenon using the Autobiographical Memory Test (AMT) to assess the specificity of autobiographical memory in the study of suicidal patients, a series of researches have replicated this phenomenon, indicating that OGM is a trait marker, as a predictor of the course of depression.
Autobiographical memory is defined as a memory of an event that occurred to him or her at a particular time and place and lasted less than one day (e.g., “my wedding ceremony”). In contrast, overgeneral autobiographical memories include categorical memories that refer to a class of generic events (e.g., “parties with my friends”) and extended memories that refer to an event lasting more than one day (e.g., “when I was on vacation last month”). Individuals with depression or trauma-related anxiety disorder, such as posttraumatic stress disorder (PTSD) usually exhibit OGM that is more general memories, less specific memories.

4.2. Mechanisms underlying OGM

Conway and his colleagues proposed Self Memory System (SMS) model in respect of autobiographical memory (Conway & Pleydell-Pearce, 2000). It is supposed in this model that autobiographical memory representation is a continuous hierarchy (see Figure 2), ranging from 1) more broad, conceptual themes in the life story such as “work theme”, “relationship theme”, to 2) lifetime periods (e.g., “my studying time in college”), to 3) general events (e.g., “parties with friends”), to 4) event-specific knowledge (i.e., specific episodic memories, such as “the party with my friends on the day of our graduation”) containing information about the sensory and perceptual aspects of unique events. A successful specific memory need to reach to the 4th level of the hierarchy (i.e. event-specific knowledge), usually via two processes: generative retrieval or direct retrieval. Generative retrieval is a top–down process down the SMS model hierarchy from the life story to event-specific knowledge bases one by one to specify the desired memory recollection. This course may take some efforts for individuals. In contrast, direct retrieval could be realized when event-specific knowledge is activated by cues in the environment, much easier than the former form of retrieval. More conceptual, intermediate representations (e.g., general events) are often activated during the early stages of generative retrieval that correspond to overgeneral memories.

Based on the Self Memory System model, the CaR-FA-X model was developed by Williams and colleagues to explain the mechanisms of OGM (see Figure 3). This model postulates that OGM results when the generative retrieval search process is aborted prematurely as a result of one or more of the three proposed mechanisms [64]. Three mechanisms delineated in the model may underlie OGM: capture and rumination, functional avoidance, and impaired executive control.

Capture and rumination are thought to occur when conceptual self-relevant information activates ruminative processes during retrieval, thereby “capturing” cognitive resources and disrupting the retrieval search. As we know, autobiographical memory is a kind of self-relevant long-term memory. Its retrieval is based on self-representation. It’s common that depressed individuals have negative self-schema, which could easily activate emotional conceptual self-representation and ruminative processes. Therefore, more abstract, conceptual negative information corresponding with self-representation could be much more easily captured by the activated emotional self-representation. More cognitive resources might have been exhausted, resulting in insufficiency of cognitive resource available to access event-specific knowledge base.
Functional avoidance refers to when the retrieval of specific memories is passively avoided as a means of affect regulation, and it is thought to occur in response to early trauma. It is hypothesized that specific details in memories could bring emotional distress about aversive experiences.
experiences, the passive avoidance of which might reduce emotional distress to some extent. It sounds reasonable when the depressed people retrieve memories with negative cues. However, it cannot explain why the depressed people also exhibit OGM when retrieving with positive or neutral cues.

**Impaired executive control** refers to when deficits in executive resources limit the ability to conduct a successful retrieval search. As mentioned, successful specific autobiographical memory retrieval involves strategic search processes that allow for current goals, the recovery of memory traces involving a rich sense of re-experience, and monitoring and other control processes [65]. Once executive control ability is impaired, it is hard for individuals to fulfill the AM task.

These mechanisms are hypothesized to contribute to OGM, alone or in interaction.

### 4.3. Instruments to measure OGM

As mentioned above, AMT designed by Williams has been regarded as a standard method to assess overgeneral autobiographical memory. On the AMT, individuals are usually visually or auditorily presented with cue words of different valences, and are asked to produce a specific memory and relevant details as many as possible related to the cue word within a given limit time (e.g., 30 s, 1 min). Williams summarized that by using AMT, eleven studies had examined the specificity of memory in people suffering from major depressive disorder (MDD) [64]. He made a conclusion that almost all the studies successfully replicated overgeneral memory in depression.

However, Raes found the Sentence Completion for Events from the Past test (SCEPT), another method to measure OGM, more sensitive in non-clinical population, relative to AMT [66]. The SCEPT comprises several sentence stems (e.g., “When I think of...”). Participants are instructed to complete the sentence stems with their past experiences. Further, they found that the omission of the instruction to be specific was the probable reason for the enhanced sensitivity. Standard AMT usually had a much more detailed instruction, which may influence individuals’ original autobiographical memory retrieval styles so as to decrease the sensitivity. So in our research we aimed to check the sensitivity of AMT without instruction, SCEPT, standard AMT and SCEPT with Specificity Instruction (SCEPT-SI) among Chinese healthy individuals or individuals with depressive mood. The results showed that under SCEPT without an explicit instruction, there was no significant difference between the mean proportions of general memory in the two groups ($t=0.52$, $P>0.05$), which was not associated with the BDI scores ($r=0.96$, $P>0.05$). Under AMT without explicit instructions, the mean proportion of general memory in the depressed mood group (DM) was significantly higher than that in the healthy control (HC) group ($t=3.86$, $P<0.01$), which was associated with depression scores ($r=0.40$, $P<0.01$). When the instruction was explicit, for the mean proportion of general memory on SCEPT-SI and the standard AMT, there were no significant difference between the two groups ($P>0.05$), and both of which were not associated with depression scores (respectively, $r=-0.04$, $r=0.09$, $P>0.05$). The conclusion in our research is that the sensitivity of AMT without explicit instruction was higher than that of standard AMT, which is in line with the previous finding Filip Rase et al [67]. However, that the sensitivity of SCEPT was higher than
that of AMT without specific instruction was not found in the results. In this research, it was also suggested that SCEPT not sensitive for the non-clinical population to assess their over-general autobiographical memory.

4.4. Neural correlates and main processes of autobiographical memory

Just try to remember the last time you went to the bookstore. If it happened long ago, you should take more effort to search it in your brain. The constructive processing would be guided by the semantic information (e.g. Bookstores), and about your own life favor (e.g. I like bookstore with an awesome environment), even about inferential processes (e.g. I went with my roommate. He also loved reading). As the course went by, the memory that mostly fit into the requirement would be constructed. However, you should correct some incorrect information (e.g. the last time I went to the bookstore alone for receipt, rather than reading). At last, I could remember much detail about spatio-temporal, sensory and perception information and so on. Tulving supposed that autobiographical memory retrieval is a dynamic course [68]. When asked to begin a specific memory task, a participant should search relevant information in his/her autobiographical memory knowledge base in order to recover memory traces. At the same time, the participant should suppress irrelevant information, clarify uncertain information, and even correct the wrong. Once successfully constructed, the memory retrieval then moved to the elaboration phase to get as much detail as possible.

Functional neuroimaging studies have detected the neural correlates of autobiographical memory retrieval. Cabeza reviewed previous studies and summarized that the main processes of autobiographical memory retrieval may encompass constructive processes, monitoring processes, self-referential processes. And he also pointed out some characteristics of autobiographical memory (emotional processes, vividness, and remoteness). As to the neural correlates for each process: left lateral prefrontal cortex is associated with the constructive processes, and ventromedial PFC with monitoring processes, medial PFC associated with self-referential processes, amygdala associated with emotion processes, visual cortex associated with the vividness of AM, hippocampus associated with remoteness of AM[69]. Similarly, St. Jacques used independent component analysis (ICA) and found four separate neural networks supporting AM retrieval: medial prefrontal cortex (MPFC) network, associated with self-referential processes, medial temporal lobe (MTL) network, associated with memory, frontoparietal network, associated with strategic search, and cingulo-operculum network, associated with goal maintenance [70]. Based on the results of normal healthy population, it is believed that OGM in depression probably has a close relationship with the failure in the main processes alone or in interaction. Lemogne proposed two modes of elevated MPFC activation in major depression, which may embody automatic aspects and strategic aspects of depressive self-focus respectively [71]. Dalgleish proved that depressed individuals exhibit OGM with impaired executive control ability in a series of behavioral experiment [72]. Whally discovered three regions of the prefrontal cortex: right inferior frontal gyrus, right middle frontal gyrus and left inferior associated with cognitive, emotional, and memory inhibition influencing specific autobiographical memories retrieval in depression using fMRI during an autobiographical memory task [73].
4.5. Application area

Research on OGM in depression is attracting increasing attention. Not only could it be a new and promising way to further discover the mechanisms of depression, but it could provide a new target for treatment. As mentioned at the beginning, OGM is a trait marker as a predictor of the course of depression, which might be an important part in the early-warning and diagnosis of depression in future.

New cognitive training has more recently been applied to a wide range of neuropsychiatric illnesses. One of which AM specificity training as a target-based tool to overcome OGM has already been paid attention and is expected to an effective method to cure depression.

Further research should deal with the neurocognitive mechanisms of OGM in depression. First, mechanisms of autobiographical memory and over-generalization of autobiographical memory call for further exploration. There is still no study to control one or more AM components directly to identify the role of each process in the course of AM retrieval. Moreover, if any molecular biological marker about AM was found, it would be helpful to targeted medication to depression. Second, more researches should be conducted on the effective cognitive training methods like AM specificity training, which is beneficial to both treatment and discovery of mechanisms of OGM in depression.

5. The disturbed interface between cognitive control and emotion processing

Major depressive disorder is characterized by a negative cognitive bias or schema, in which depressed patients are prone to negative perception bias or show difficulty in disengagement from depression-related information[74] or diminished capacity to experience pleasure (anhedonia). Although numerous studies have examined the neural basis underlying the negative cognitive bias of depression, the mechanisms remain unclear. In general, the negative cognitive biases in depression are facilitated by increased influence from subcortical emotion processing regions combined with attenuated top-down cognitive control.

5.1. Excessively emotion-processing

Previous study focused on the bottom-up emotion-processing (most notably the amygdala and fusiform gyrus) to explore the neural mechanism of depression. The hyperactivity of amygdala and fusiform gyrus is obviously correlated with the bias reflects excessive bottom-up responses to negative stimuli.

The amygdala, a brain structure which is involved in detecting emotion (for example, salience detection), interprets and maintains the emotional quality of the stimulus. Amygdala activity increases in healthy individuals during processing of emotional information. Compared to healthy controls, individuals with depression show increased activity during the perception and evaluation of, and response to negative emotion-inducing stimuli. Recent studies explored
the behavioral characteristics and neural mechanism with a validated emotional face-matching task[75]. Although both MDD and HC groups were not significantly different in RT and percent correct for faces, or shapes, the MDD relative to HC subjects showed increased activity in bilateral extended amygdale during performance of a validated emotion-processing task. Besides, the MDD showed more task-related co-activation of the subgenual cingulate, which is involved in processing negative self-referential information; and less co-activation of the supragnenual cingulate, which is involved in the cognitive control of emotion. Greater depressive symptom severity correlated positively with decreased FC between bilateral extended amygdala (EA) and supragnenual cingulate in MDD subjects. Furthermore, the increased amygdala reactivity to negative stimuli is not only found in MDD, but also in BD (Bipolar Disorder) [76]. Other studies also indicated that amygdala hyperactivity is a neural substrate of biased attention [77, 78] and biased memory for negative stimuli[79]. Similar result was found in unmedicated remitted depressed individuals. Following sad mood induction, bilateral amygdala response during encoding of valenced words predicted increased recall of negative self-referent words for a subset of remitted depressed participants[80]. This association was not present before the sad mood induction and was not evident in individuals without a history of depression, regardless of mood state. These results suggest a role for amygdala in modulating mood-congruent memory during transient sad mood in individuals vulnerable to depression relapse.

Besides amygdala, the negative cognitive bias also linked to deficits in fusiform gyrus. Using event-related fMRI, neural responses to happy and sad facial expressions were measured in healthy individuals and individuals with major depressive disorder [78]. The study indicated that depressed but not healthy individuals demonstrated linear increases in response in right fusiform gyrus to expressions of increasing sadness. Besides, similar results was found in the neural responses of high-risk population of depression compared to low-risk group (by virtue of high and low neuroticism scores; high-N group and low-N group respectively) during the presentation of fearful and happy faces using fMRI [81]. The results indicated that the high-N group demonstrated linear increases in response in the right fusiform gyrus and left middle temporal gyrus to expressions of increasing fear, whereas the low-N group demonstrated the opposite effect. Besides, the high-N group also displayed greater responses in the right amygdala, cerebellum, left middle frontal and bilateral parietal gyri to medium levels of fearful v. happy expressions. Furthermore, the activation during negative emotional response in right fusiform gyrus reduced after antidepressant treatment.

Excessively emotion-processing models have established that the bias reflects excessive bottom-up responses to negative stimuli[74], linked to hyperactivity in the limbic regions, such as amygdala, fusiform gyrus. Individuals with depression show increased activity during the perception and evaluation of, and response to negative emotion-inducing stimuli. Therefore, they experience further negative emotion, leading to more profound depression.

5.2. Impaired cognitive control

Previous study also focused on a diminishing the top-down cognitive control (most notably prefrontal cotex) to explore the neural mechanism of depression. This attenuation in cognitive
control seems to be region specific (for example, the MPFC for self-referential schemas, the DLPFC for rumination and biased processing and the VLPFC for biased attention) and curbs the top-down relationship (through the ACC and thalamus) with pertinent subcortical regions.

Compared to healthy subjects, subjects with midlife major depression showed a failure of hippocampal and anterior cingulate activation underwent positron emission tomography imaging during a control task and verbal encoding of a paragraph[82]. Another study explored relationships between amygdala and DLPFC activity during emotional and cognitive information processing in unipolar depression [83]. The results indicated that depressed subjects displayed decreased DLPFC activity on the digit-sorting task. It is consistent with previous studies[76]. Besides, one study recorded 128-channel event-related potentials while study Patients with MDD and healthy comparison subjects performed a Stroop task, modified to incorporate performance feedback[84]. The results indicated that unmedicated patients with MDD showed reduced accuracy and potentiated error-related negativity immediately after committing errors, highlighting dysfunctions in the automatic detection of unfavorable performance outcomes, and abnormal reaction to committing errors was accompanied by hyperactivation in rostral ACC and medial PFC regions 80 milliseconds after committing errors and a failure to recruit dorsolateral PFC-based cognitive control, which is consistent with previous results.

Impaired cognitive-control models have pointed out that the bias reflects impaired top-down cognitive control[85, 86], linked not only to reduced activities in cortical regions, including DLPFC, anterior cingulate cortex (ACC), and rostral ACC[84, 87, 88], but also to reduced N450 and N200 amplitudes[84]. To maintain the same level of performance as healthy subjects, individuals with major depression need increased effort to recruit more cerebral resources, suggesting that depression may impair the top-down cognitive control capacity of afflicted patients. With limited top-down cognitive control from the PFC, the consequences of maladaptive bottom-up activity persist, including enhanced amygdala reactivity (which contributes to biased attention and cognitive processing).

5.3. The disturbed interface between cognitive control and emotion processing

As noted earlier, some studies may explain the cause of depression from the perspective of abnormal emotional processing or impaired cognitive control. However, it is unclear whether emotional processing and cognitive control affect the negative cognitive bias independently or reciprocally. To answer this question, a number of researches have been carried out. Siegle et al. reported increased activity in the amygdala in response to personally relevant negative words (personal relevance rating of words) and dorsal lateral prefrontal cortex (DLPFC) hypoactivity in a cognitive control task (digit sorting)[83]. However, because the two tasks are carried out separately, it is difficult to observe how emotion processing interacts with cognitive control. Subjects were asked to respond to several targets in the context of emotional or neutral stimuli. They found that processing of emotional contexts could interfere with the processing of cognitive control; emotional interference exerted a greater influence on depressed subjects. However, Goldin et al. found that reappraisal (a strategy of cognitive control) was associated with early (0–4.5 s) prefrontal cortex responses and decreased amygdala responses, suggesting
that cognitive control played an important role in mediating emotional processing[89]. Notably, by combining emotional-processing task with cognitive-control task (emotion-interference task), Fales et al. found that depressed patients showed hyperactivity in emotion-processing regions, including the amygdala, and in cognitive-control regions, including the DLPFC and dorsal anterior cingulate cortex (ACC). Their results suggest that these processes might interact with each other[89]. Although more attention was paid to activity alterations in emotion-processing and cognitive-control regions in Fales’ study, the relationship between bilateral emotion processing and bilateral cognitive-control regions was somehow ignored.

Therefore, we took bilateral amygdala as regions of interest (ROIs) to determine the relationship between bilateral emotion-processing and bilateral cognitive-control regions[90]. The results indicated that depressed patients showed abnormal activities in bilateral amygdala and the right DLPFC. In addition, a significant correlation was found between the right amygdala and the right DLPFC when subjects observed the happy faces. The results suggest that the dysfunction in positive emotion-processing and cognitive-control regions may reciprocally affect negative cognitive bias. Additionally, altered positive emotional interference processing in the fronto-limbic brain circuitry might be another cause of negative cognitive bias that finally leads to depression.

To sum up, depression is characterized by a negativity bias which is a stable factor of it. The bias reflects enhanced bottom-up responses to affective stimuli, linked to deficits in amygdala and fusiform gyrus function. Alternatively, the bias also reflects impaired top-down cognitive control, linked to deficits in dorsolateral prefrontal cortex and anterior cingulate function. We recommended a new hypothesis that the occurrence of depression is caused by interaction of dysfunction in positive emotion processing brain regions and deficits in cognitive-control brain regions.

6. Future trends and conclusion

In summary, several lines of research point to separate mechanisms (for example, over generalized autobiographical memory, negative attention bias, abnormal emotion regulation, deficits in cognitive control of emotion, negative appraisal and reappraisal), in individuals with depression, that increase the salience of negative stimuli and decrease the salience of positive or rewarding stimuli. As a result, a person with depression displays a cognitive bias towards negative information and away from positive information, thus contributing to the maintenance of a depressed mood state.

In parallel with existing neurobiological models of depression that focus on affective symptomatology, Beck’s cognitive–neurobiological model suggests that cognitive biases in depression are due to maladaptive bottom-up processes that are generally perpetuated by attenuated cognitive control, and has provided an evidence-based framework to conceptualize and treat major depressive disorder. While Beck’s cognitive model provides new features and benefits to understanding the symptoms and underlying neural substrates for major depressive disorder. The mechanism of various components leading to depression is still vague.
Future research should seek to identify which neurobiological mechanisms contribute to the selective processing towards negative, and away from positive, environmental stimuli.

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Author details

Zhengzhi Feng1*, Xiaoxia Wang2, Keyu Liu1, Xiao Liu1, Lifei Wang3, Xiao Chen1 and Qin Dai4

*Address all correspondence to: fzz@tmmu.edu.cn

1 College of Psychology, Third Military Medical University, Chongqing, China

2 Department of Basic Psychology, College of Psychology, Third Military Medical University, Chongqing, China

3 Department of Developmental and Educational Psychology, College of Psychology, Third Military Medical University, Chongqing, China

4 Department of Nursing Psychology, School of Nursing, Third Military Medical University, Chongqing, China

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