

# Depression and Cognitive Impairment: Current Understanding of Its Neurobiology and Diagnosis

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**Background:** Eye movement is critical for obtaining precise visual information and providing sensorimotor processes and advanced cognitive functions to the brain behavioral indicator.

**Methods:** In this article, we present a narrative review of the eye-movement paradigms (such as fixation, smooth pursuit eye movements, and memory-guided saccade tasks) in major depression.

**Results:** Characteristics of eye movement are considered to reflect several aspects of cognitive deficits regarded as an aid to diagnosis. Findings regarding depressive disorders showed differences from the healthy population in paradigms, the characteristics of eye movement may reflect cognitive deficits in depression. Neuroimaging studies have demonstrated the effectiveness of different eye movement paradigms for MDD screening.

**Conclusion:** Depression can be distinguished from other mental illnesses based on eye movements. Eye movement reflects cognitive deficits that can help diagnose depression, and it can make the entire diagnostic process more accurate.

**Keywords:** depressive disorder, cognitive impairment, eye movement, biological marker, neurology

## Introduction

Major depressive disorder (MDD) is a psychological disorder characterized by depression lasting longer than 2 weeks, along with emotional pain, dysfunction, health issues, suicide, and other conditions. MDD is a prominent cause of psychiatric disability as well as a significant financial burden.<sup>1</sup> There is no objective biomarker that detects serious depression in the clinical environment, despite physiology and neuroimaging research demonstrating modifications in people with depression.

Cognitive impairment is a common and typically persistent primary depression symptom, accounting for a disproportionately high percentage of patients who have not completely healed their psychosocial function.<sup>2</sup> According to the Research Domain Criteria (DOC), cognitive impairment is among the most prominent components of MDD.<sup>3</sup> However, the typical cognitive symptoms of people with depression are fewer than those of people with schizophrenia or bipolar disorder.<sup>4,5</sup> Cohort studies have shown that cognitive impairments such as inattention, poor memory, and decision-making difficulties are common symptoms of patients with major depression.<sup>3,6</sup> Valid and effective cognitive dysfunction screening techniques are critical for detecting and treating cognitive dysfunction in MDD.<sup>7</sup> Existing clinical interviews are subjective evaluations of cognitive function (eg, COBRA/strengths and difficulties questionnaire), which are affected by feelings and emotions and are not as stable as objective tests. According to the literature, cognitive dysfunction can have a negative impact on organizational, occupational, and social functions.<sup>8,9</sup> In addition, cognitive recovery is increasingly becoming a major treatment goal for patients with psychiatric disorders, particularly MDD.<sup>10</sup> Therefore, it is imperative to study cognitive function in depression.

The evaluation of neurological data yielded valuable information for the successful screening and assessment of MDD's cognitive symptoms. Cerebellar-cerebral dynamic FC of the cerebellar subregions communicating with the

executive, default-mode, and affective-limbic networks, for example, was impaired in individuals with MDD, according to earlier results.<sup>11,12</sup> EEG data report state and trait abnormalities in resting-state brain activity in MDD.<sup>13</sup> In functional near-infrared spectroscopy (fNIRS), reduced Hb changes during cognitive engagement have been identified as potential biomarkers for depressive disorders.<sup>14</sup> The neurological study of depression is still at the stage of scientific research and is not widely used clinically due to factors such as its high cost and interference from external factors. It is not known whether the accuracy of MRI and fNIRS in the population is consistent with the experimental population. To summarize, identifying cognitive function in people with depression necessitates more sensitive methods than those now available. Eye movement has received much interest recently in the field of neuroimaging.

Eye movement is critical for obtaining precise visual information and providing sensorimotor processes and advanced cognitive functions to the brain behavioral indicator.<sup>15</sup> In 1908, Diefendorf and Dodge were the first to describe the smooth pursuit eye movement characteristics of participants with “dementia praecox” and “bipolar disorder”.<sup>16</sup> Scholars have found that abnormal eye movements may be a reliable biomarker for schizophrenia.<sup>17</sup> Similar to schizophrenia, patients with depression also have cognitive impairment. Researchers have started to pay more attention to eye movement in people with mental illnesses. It has been suggested that the abnormalities of the oculomotor system seen in patients with affective disorders may not be different from other psychomotor disorders.<sup>18,19</sup> However, Carvalho came to a different conclusion that eye movement paradigm tests can assist in distinguishing depression from bipolar disorder.<sup>20</sup> The reliability of using eye movements to study cortical mechanisms of cognitive function as a new approach for studying advanced cognitive functions is unclear yet.<sup>21</sup>

The basic features of eye movement include fixation, smooth pursuit eye movement, saccades. Scholars discovered that scan path length was substantially connected with cognitive measures of MDD in recent eye movement research.<sup>22</sup> The study found no effect of the study drug on eye movements in patients with psychotic affective disorder. This information aids in the detection of impaired eye function and the provision of suitable therapy in cognitive studies.<sup>23</sup>

In this paper, our aim was to review previous clinical studies, reviews, and meta-analyses on saccadic eye movement paradigms (including fixation, smooth pursuit eye movements, memory-guided saccade task and free viewing task) in major depressive disorder. To summarize a narrative review of the application of the eye movement features in depression. In each paradigm, our current research is divided into two categories: features of eye movement paradigms in depression and neurological mechanisms. Then, we provide perspectives for future research.

## Fixation

A fixational eye movement occurs when a subject attempts to control their gaze within a restricted space. A person's eye movements during fixation are caused by the activity of the vestibular and visual compensatory systems. Fixational eye movement can be divided into three categories: microsaccades, ocular drift, and tremor.<sup>24</sup>

The concept of ocular drift is commonly believed to involve a very slight and very slow movement of the eyes. A typical classical study reported amplitude values ranging between 1.5 and 4 feet, and median velocities of approximately 4 feet per second.<sup>25</sup> We generally call the two maintained fixation. Since there is a small difference in drift and tremor, there is less eye movement and current acquisition equipment, fewer studies have been conducted. The occurrence of drifts during fixation selectively activates V1 neurons.<sup>26</sup>

Microsaccades are miniature replications of the rapid gaze shifts that humans use to explore visual environments (saccades). Studies on maintaining fixation have shown that saccades exceed 12–15 minutes of microsaccades in size. Microsaccades may serve the function of bringing the eye to a series of locations of interest in a similar manner to a larger saccades.<sup>27</sup> According to some researchers, microsaccades is associated with attentional shifts, The oculomotor system is subconsciously activated by covert attention in microphthalmoplegia.<sup>28</sup> As microsaccades provide a continuous, online measurement of the oculomotor system, they can provide insight into a wide range of cognitive functions, for example, spatial attention,<sup>29</sup> temporal attention<sup>30</sup> and working memory.<sup>31</sup> Microsaccades are generated by the superior colliculus (SC), a retinotopically organized structure involved in voluntary saccade target selection.<sup>32,33</sup>

During the resting stability test, Takahashi<sup>34</sup> found no significant differences between the depressed and healthy control groups. However, saccal amplitudes were found to be greater in depressed patients by.<sup>35</sup> Similarly, Li agrees that there are differences in the fixation task between depression and normal individuals. Compared to healthy controls, patients with

depressive disorder showed more fixations, shorter fixation durations, more microsaccades and longer saccade lengths<sup>22</sup>. Among populations with mental disorders, fixed paradigm experiments have been studied less extensively.

As physical research techniques are developed, a greater number of studies are expected to reveal 1. Why do fixed eye jumps occur? 2. Are fixational eye jumps characterized differently by different mental disorders? 3. What's the connection between fixation gaze and attentional bias?

## Smooth Pursuit Eye Movements

Since the rediscovery of smooth pursuit eye movements in schizophrenia, psychiatry has been researching eye movement.<sup>36</sup> The smooth pursuit eye movements (SPEMs) task is a test of the central vestibular system that assesses the patient's ability to accurately track visual targets in a smooth, controlled manner.<sup>37</sup> The SPEMs task assesses depression's cognitive control, influenced by the attention process.<sup>38,39</sup>

SPEMs occur in relative motion between the eyes and the observed object, maintaining the eyes fixed on the object and the eyeball following the object's movement. Areas in the cerebral cortex, such as the middle temporal lobe area and the right temporoparietal junction area, may control SPEMs.<sup>40</sup> SPEMs are controlled by a cerebro-pontocerebellar pathway that bypasses the longer-standing centers for saccades in the brainstem tegmentum.<sup>41</sup> The frontal eye field (FEF), middle superior temporal area (MITI), lateral intraparietal cortex, dorsolateral pontine nucleus, and other cortical regions associated with eye movement have been discovered in previous neurophysiology and brain imaging studies in monkeys and humans.<sup>42-44</sup> The pursuit characterization of FEF with microstimulation has been linked to the tracking eye movement gain setting for the pursuit eye movement in monkeys.<sup>45</sup> The middle temporal area serves as a global motion processor, assisting target movement and causing reverse smooth tracking errors.<sup>41</sup> The cerebellum creates SPEMs by sending messages from these cerebral cortexes to the brain. In addition to pursuit-related neurons, the lateral intraparietal<sup>46</sup> and ventral intraparietal<sup>47,48</sup> areas have also been investigated. Signals related to SPEMs have been observed in the intermediate and medial parts of the dorsal pontine nucleus.<sup>49</sup>

MRI revealed that multiple brain regions are significantly impaired in MDD patients. Gray matter changes in the frontal lobe, thalamus, and temporal lobes (eg, the hippocampus and amygdala) correspond to eye movements.<sup>50</sup> Furthermore, aberrant brain activity in the prefrontal cortex was discovered.<sup>51</sup> There is a neurological basis allowing for speculation about whether changes in depressed brain regions cause changes in SPEMs. Coincidentally, after analyzing the effects of electroconvulsive treatment (ECT) on SPEMs in severe MDD, Malaspina et al concluded that SPEM abnormalities might be a state marker in severe MDD.<sup>52</sup>

Thirty patients with major depression were evaluated three times for smooth pursuit eye movement during a four-week therapeutic study, and most key indicators were unaffected by neuroleptic medication or clinical conditions.<sup>17</sup> Thus, SPEMs are considered one of the stable features of eye movement in depression. In the SPEMs, the significant eye movement characteristics in depression are the duration of saccades, peak saccade velocity<sup>34</sup> and decreased gain.<sup>53</sup> When compared to the healthy controls (HCs), the SPEMs in patients with depression have a high peak speed. Takahashi argues that peak saccade velocity in the SPEMs task is one of the potential biomarkers to distinguish between MDD patients and HCs. Research has shown that peak saccade velocity is 72.1% accurate in discriminating between MDD patients and HCs,<sup>34</sup> and the ROC curve indicates that this feature could be used to distinguish MDD patients with moderate accuracy. A study showed more fixation numbers and shorter fixation durations in MDD patients.<sup>54</sup> These findings support the concept that SPEMs are a "state marker in severe major depression".<sup>52</sup>

However, a recent study also concluded that patients with major depressive disorder, bipolar depression, and mania have similar oculomotor dysfunction in the SPEMs task.<sup>54</sup> Whether there are differences in the eye-movement characteristics of depression needs to be further explored.

## Saccadics

Saccadic vision is a rapid gaze shift in which the point in the center of the retina is relocated to a new object in the visual scene to achieve accurate and clear vision. Participants in the prosaccade tasks were instructed to pay attention to new stimuli in their environment. In the antisaccade tasks, the subject looks at a fixation point and upon presentation of a visual target, participants were asked to ignore the target and look in the opposite direction.<sup>55</sup> In view of the fact that forward prosaccade is often compared with antisaccade tasks, they will be discussed together.

The saccadic network in marmoset monkeys was investigated utilizing task-based fMRI, which revealed that the task elicited a strong visual-saccadic topology.<sup>56</sup> There are several key distinctions between saccades and smooth pursuit eye movement. Both types of eye movements are regulated by neural physiological levels and two types of eye movements.<sup>41,57</sup> Saccadic eye movements, like smooth pursuit eye movements, are linked to the FEF, which is responsible for coding and triggering the rhythm.<sup>58</sup> When deliberately or reflexively glancing around a room, large motions occur. Furthermore, the velocity of saccades is unaffected by deliberate effort or experience.<sup>59</sup> The initiation of the saccade, a condensing cognitive control, is subject to the actions of heteromodal neocortical regions, which are aided by other brain regions, additional neural regions, the striatum, and more typical sensorimotor regions.<sup>60</sup>

Saccades engage a core eye-movement network, including the posterior parietal cortex (PPC), FEFs, supplementary eye fields (SEFs), basal ganglia, the brainstem (eg, superior colliculus), and the cerebellum.<sup>61</sup> The malfunctioning neocortical area, other nerve areas, the striatum, and more conventional sensorimotor areas all contribute to the start of saccades. During both comparisons, patients had longer antisaccade latencies and lower antisaccade peak velocities compared to 60 healthy controls (who were matched the precuneus, supplementary eye fields (SEF), and FEF showed anti-saccade-related activity, while the prefrontal cortex (PFC) showed anti-saccade-related activity during a single task comparison.<sup>61</sup> FEF activity was related to whether the response to cognitive inhibition was effective, and it plays a critical role in the cortical oculomotor network via mediating visuomotor transformations for controlling saccadic eye movements and spatial attention orientation.<sup>62,63</sup> The superior colliculus (SC) is a brainstem center of saccade control.<sup>64</sup> Between the FEFs and the SC, there are two signal transmission channels. The direct signaling of FEFs to the SC is one example. Another option is to take a circuitous route through the basal ganglia. The indirect pathway is through the substantia nigra, which suppresses SC activity.<sup>65</sup> In contrast to SEF and FEF activation, in the process of antisaccade tasks, activity in the dorsolateral prefrontal cortex (DLPFC) is involved as an inhibitory component, according to neurophysiology and human lesion evidence.<sup>60</sup> Observation of a patient with DLPFC lesions demonstrated that some DLPFC neurons activate exclusively to anti-cues, with high rates of failure to suppress saccades to targets.<sup>65</sup> Various approaches have been proposed, and MDD has been linked to increased inhibitory control and reduced motor activity. Increased impulsivity, on the other hand, has also been noted.<sup>66</sup> As a result, researchers associate SEF, FEF, and DLPFC with depression and explore their correlation. An increase in right dominant blood flow occurred with prosaccade and anti-eye skipping tests. Patients with MDD had a smaller increase in right dominant blood flow than controls. Patients had a higher error rate than controls in the anti-eye jump test but not in the prosaccade test. The smaller blood flow response may reflect the expected diminished activation of the dorsolateral prefrontal and inferior parietal cortices in MDD. In addition, patients with MDD showed an increase in right dominant blood flow during the prosaccade and antisaccade tests, but this increase was smaller than that in controls. This phenomenon may reflect diminished anticipatory activation in dorsolateral prefrontal and inferior parietal cortices in MDD.<sup>67</sup>

Researchers discovered that 60 MDD patients had longer antisaccade latencies and lower antisaccade peak velocities than 60 HCs (who were matched by gender, age, and years of education).<sup>22</sup> In the experiment, participants first fixed their eyes on the black fixation point “+” in the center of the white screen. Participants were asked to gaze at the stimulus (a solid or hollow dot) as fast and efficiently as possible (if the motivation was a solid dot) or to look at the opposite side (if the stimulus was a hollow dot) when the target stimulation appeared. Patients with major depression had significantly longer antisaccade latencies and lower peak antisaccade velocities, implying that aberrant antisaccade brain circuits resulted in decreased eye movement inhibitory functioning. This indicates damage to cognitive function, which is thought to be a sign of depressive disorder.<sup>68,69</sup> FEF activity corresponds to the success or failure of the response to cognitive inhibition and plays a crucial role in the cortical oculomotor network in mediating visuomotor transformations for managing saccadic eye movements and in the orientation of spatial attention.<sup>62,63</sup> Patients had significantly higher reaction times (RTs) and increased rates of response suppression errors<sup>70</sup> (Mahlberg et al, 2001, Sweeney et al, 1998); thus, patient groups needed more corrective saccades to reach the target than controls (Mahlberg et al, 2001, Sweeney et al, 1998). Depressed patients also have a higher rate of anti-eye darting errors.<sup>67</sup> These findings support the idea of active control impairment in MDD. There are conflicting views on research on eye darting. Carvalho<sup>70</sup> discovered that depression lengthens the latent duration of the pro-saccade task, but Li<sup>22</sup> suggested that prosaccade amplitude correlates with anxiety symptoms, not depression symptoms. The error rate on the pro-saccade task in depressed patients is similar to that of healthy people.<sup>67</sup>

A recent study also found that MDD patients had a longer duration of saccades.<sup>34,71</sup> The anomalous secular organization of thinking and behavior that was reduced in MDD could be explained by temporal preparation mechanisms.<sup>66</sup> Compared to depression patients, depressed patients with suicidal behaviors exhibited fewer errors and a longer time to correct them.<sup>72</sup> These findings give credence to the theory that saccades can represent a reduced cognitive function in depression. Furthermore, in addition to being an assessment tool, some researchers have begun to evaluate the possibility of predicting different treatment responses based on AS parameters.

## Free Viewing Task

We discovered that depressive patients frequently have difficulties understanding facial emotional expressions and have biased facial emotion detection.<sup>73,74</sup> Excessive attention to negative information is one of the hallmarks of depressed cognition.<sup>75</sup> In order to benefit the patients with depressive disorder, the researchers developed the free viewing task by taking advantage of the skipping-eye feature.

Free-viewing paradigms are generally used to detect attentional bias and allow the patient see pictures presented on the computer screen, which displays sad, angry, joyful, and neutral expressions simultaneously. The amygdala, orbitofrontal cortex, primate prefrontal cortex (PFC), and anterior cingulate cortex are consistently activated during emotional face processing.<sup>76,77</sup> Patients with lesions in both the orbital and medial PFC demonstrate a range of social cognition characteristics.<sup>78</sup> The term “vmPFC” refers to an interconnected regional network in the lower medial and orbital prefrontal cortex.<sup>79,80</sup> During the active regulation of negative emotions, a smaller area in the posterior ventral vmPFC and the left amygdala displayed convergent activity.<sup>81</sup> Furthermore, investigations have demonstrated that the amygdala is linked to the medial, lateral (middle frontal and inferior gyrus), and orbitofrontal/ventromedial regions of the PFC.<sup>82</sup> A monkey study found that amygdala lesions could cause improper social and emotional behaviors in a context-inappropriate manner.<sup>83</sup> In depressed individuals, the amygdala may respond to both positive and negative emotions.<sup>84</sup> When processing fearful faces, higher levels of depression were associated with decreased left putamen–right amygdala functional connectivity.<sup>85</sup>

Free viewing eye-movement studies of depression in emotion recognition are consistent with neurological findings. Depression leads to persistent attention to unfavorable information during development and maintenance.<sup>86</sup> Compared to HCs, depressed individuals are generally less focused on the eyes and mouth, representing an avoidance of facial features.<sup>87</sup> In neurology, researchers found that the severity of depression was associated with increased brain activity in mood control and emotion-sensitive areas.<sup>88</sup> A study found that the total dwell times and fixation on threatening, sad, and optimistic naturalistic face images revealed good to exceptional reliability for attentional biases for dynamic images.<sup>89</sup> Positive attentional bias drastically decreases regardless of age, but negative attentional bias increases.<sup>89,90</sup> A study investigated the emotional information recognition characteristics of patients with depression; eye movements showed that they were slower to detect positive emotion.<sup>85</sup> Patients with MDD spent longer on sad faces in an eye movement test with equally divided viewing periods between happy and neutral faces.<sup>90,91</sup> Another result showed longer duration times for null events and saccades and no significant difference between the time spent on different emotional expressions.<sup>92</sup> However, it has been suggested that depressed and healthy individuals show a high degree of similarity when visually searching for clusters of facial emotional expressions; there is no difference in reaction time to all emotional target faces.<sup>93</sup>

Attentional bias toward happy faces remained reduced, and there was still a deficit in positive attentional bias during depression remission.<sup>94,95</sup> However, there are different views on whether the negative attentional bias of depressed patients is improved. Li<sup>94</sup> thought there were no significant differences in first fixation location and initial attentional maintenance to face pictures; nevertheless, Isaac<sup>95</sup> found remitted depression patients to have longer fixation times for all emotional expressions compared to HCs. More research is needed to determine whether a reduction in processing positive information is associated with a history of depression and whether it can be a basis for assessing the risk of relapse and continuation of treatment for depression.

Emotion recognition bias is linked to an enlarged DLPFC and deactivated amygdala.<sup>96</sup> According to the available neuroimaging evidence, the phenomena during emotional processing comprise general striatal and limbic modifications as well as particular, disorder-specific alterations in the prefrontal areas.<sup>97</sup> Researchers verify that depression can re-emerge through neurological changes reflected in the appearance of negative attentional bias.<sup>98</sup> In recent years, it has also been found that eye tracking training can be an important therapeutic target by enhancing cognitive function in patients with depression<sup>99</sup> and changing the patient’s mood.<sup>99</sup> Poletti<sup>100</sup> found that the attention bias in depression can be changed by reward-based eye

movement training. The rapid improvement in positive attention bias can predict the later treatment effect of clinical depression reduction. Eye tracking tests are used to determine whether selective serotonin reuptake inhibitor (SSRI) medications may reduce depression's negative attention bias and generate therapeutic responses. Patients demonstrated an increased tendency to concentrate on happy images and a decreased tendency to concentrate on negative images after eight weeks of SSRI medication.<sup>12</sup>

In summary, the free-viewing eye movement experimental paradigm is of great interest both in the detection and treatment of cognitive impairment in depression and needs to be explored in greater depth by researchers.

## Memory-Guided Saccade Task

Moving the eye to a memory region that flashes momentarily after a delay is named the memory-guided saccade (MGS) task. Participants are required to keep their eyes on the central gaze point. During this time, the target appears outside the center gaze point, and participants are not allowed to stray to the target. After the central gaze point disappears, the subject needs to scan to the location just remembered. This is a delayed oculomotor response task that has been widely utilized in primates to explore spatial short-term memory.<sup>101</sup> Specific characteristics of MGS might depend on whether the subject has prematurely erroneous saccades toward the stimulus, a so-called disinhibition error.<sup>102</sup>

The memory-guided saccade is seen as a full change. The task-dependent timing of this transformation process throughout a memory delay between vision and action was shown by a new set of spatial models (from target to future gaze coding).<sup>103</sup> The frontal eye field is essential for transitioning from perception to movement.<sup>104</sup> Researchers started a new study to provide first-hand knowledge about how neurons interact and cooperate. According to one theory, one possible interpretation is that when motor neurons become active after the memory delay, other neurons with mixed coding on behavior (perhaps through selective gating) have less influence over behavior. As a result, there is a stronger link between their firing rate and gaze mistakes.<sup>105</sup>

When two male cynomolgus macaques (*Macaca fascicularis*) performed a long-duration memory-guided saccade task, local field potentials were recorded. Frontal memory circuits synchronized in response to stimulus presentation and memory encoding; however, they gradually desynchronized to below the baseline level over a long memory period.<sup>106</sup> The dorsal pulvinar in spatial coordinate transformations<sup>107</sup> and the mesial temporal lobe are associated with the onset of visual stimuli (image onset).<sup>108</sup> The intermediate layers of the SC integrate inputs from visual areas, frontal-parietal regions, and basal ganglia and project directly to the premotor circuit in the brainstem to initiate the orienting response, including not only shifts of attention and gaze but also pupil dilation.<sup>109</sup> Chin-Wang<sup>110</sup> found that pupil constriction occurred significantly after the presentation of the bright patch compared to the dark patch at the spatial location of the target in MGS.

Memory saccades are also being explored more extensively in other disorders. In patients with X-linked dystonia-parkinsonism, the amplitude of memory-guided saccades was reduced, and the latency was prolonged.<sup>111</sup> Patients with cerebellar dysfunction in clinically isolated syndrome had worse MGS latencies and mistake rates and had lower working memory, executive function, and information processing speed *z* scores than patients without cerebellar dysfunction in a clinically isolated condition.<sup>112</sup> On the memory-guided saccade task, depressed patients showed an increased error in their memory for spatial location information, which implies inadequate spatial working memory.<sup>71</sup> However, more studies on memory saccades in people suffering from depression are needed to verify this result.

## The Integration of the Multiple Modalities Model

The role of eye movement in diagnosis still needs to be explored. According to a depression experiment, the scan path length of the free-viewing test and peak saccade velocity of the smooth pursuit test resulted in 81% sensitivity and 69% specificity.<sup>34</sup> Others believe that compared with MRI, eye movement measurements are not specific to major depressive disorders. Research has shown that patients with depression and bipolar disorder or schizophrenia have varied preferences in free-view tasks.<sup>76,113</sup> Eye movement as a diagnostic tool is still problematic due to tiny sample numbers.

Researchers have combined several biomarkers and classifiers with machine learning algorithms to boost diagnostic accuracy. A content ensemble method based on electroencephalogram (EEG) and eyes movement data has been proposed based on a cross-sectional study. The static and dynamic ensemble methods attain 82.5% and 92.65% accuracy, respectively.<sup>114</sup> Another study added galvanic skin reaction, and the highest classification score was obtained by logistic

regression algorithms, with an accuracy of 79.63%.<sup>115</sup> Low-level eye movement characteristics using a hybrid classifier with 70% accuracy and 75% accuracy were obtained using statistical metrics such as Gaussian Mixture Models and Support Vector Machines.<sup>116</sup> Thus, the integration of multiple modalities would improve the classification models' performance.

However, the combination of functional near-infrared spectroscopy with eyes movement to evaluate cognitive function is still in the research stage. The two technologies were utilized to investigate behavioral and neurophysiological differences.<sup>117–119</sup> Multimodal analyses imply that the demand for increased attentional effort and alertness of visuomotor control causes activity in the right superior parietal lobule to rise, which is a good candidate for objectively measuring visuomotor cognitive load. This combined application is currently being used in research on the cognitive development of infants and young children, and there are numerous studies on teenage education.<sup>120,121</sup> However, it has not been applied to the field of psychiatry. It may be feasible to distinguish between attention and cerebral blood flow in patients with mental disorders both at rest and when doing tasks. On the other hand, combining these methods can aid in the development of a multimodal diagnosis model for mental disease.

Event-related potential and eye movement technologies provide novel means to objectively document receptive language processing in people with neurodevelopmental disorders such as autism.<sup>122</sup> The results of one study showed that inconsistent speaker-meaning sentences generated a higher N400 than anomalous sentences. Eye movements showed an evident bias toward the voice-consistent object.<sup>123</sup> Another method analyzes fundamental visual and oculomotor processes by combining eye movement, neurophysiological assessment, and computer modeling. The sensory/eye movement and semantic level barriers of schizophrenia are reflected by the ability to read fluently, which appears as changes in saccade number and fixation duration. The outcome explains the cognitive impairment of schizophrenia.<sup>124</sup>

More neuroimaging and genetic information are being included in diagnosis and prediction models to reduce erroneous diagnosis and ineffective treatment trials for depression. The current model integration type is limited to a single biological marker, and more biological markers need to be integrated.

## Future Directions

This paper reviews the neurological basis of eye movements as an aid in the diagnosis of depression and addresses the current state of research on it. The majority of available eye movement paradigms studies conclude that depression differs from other psychiatric disorders in its oculomotor features, but it is not proven that these features can be used as diagnostic criteria. Future research should improve the eye-movement paradigm to make it relevant to depression based on neurobiological findings.

Eye movement has been a significant medical diagnostic tool for a long time. Neuroimaging studies have demonstrated the efficacy of eye movement paradigms for MDD screening. Eye movement reflects cognitive function deficiencies that can aid in the diagnosis of depression, and it may make the whole diagnosis process more accurate, less cumbersome, and even concealed for the patient. Current research on eye movement in depression has concentrated primarily on antisaccade and free eye movement, and more diverse experimental paradigms should be explored to reflect cognitive impairment. More factors, such as disease subtypes, age and sex, also need to be explored and studied in a more detailed way. The combination of eye movement and other technologies to create multimodal models through algorithms is the general trend that will change current diagnostic methods.

Although a limited number of studies are already confirming this, more research is required to demonstrate the therapeutic feasibility of eye movement. This would be a major advancement in possible neurocognitive alteration of the brain through the eyes. Eye movement characteristics are associated with cognitive impairment in the depressive disorder. However, this still needs to be investigated in longitudinal studies. Eye movement has the advantages of safety, reliability, universality and low cost and will be widely used in clinical diagnosis in the future.

## Limitations

The field of eye movement is one of the most diverse and heterogeneous in the cognitive sciences. Current eye movement measures may not fully assess this neurocognitive domain. Additionally, these neuropsychological measures may not be ecologically valid. Our scoping review is likely generalizable to journal articles and systematic reviews acquired through the North China University of Technology Open Access Policy.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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