Visual electrophysiology and neuropsychology in bipolar disorders: A review on current state and perspectives

Katelyne Tursini a, b, Steven Le Cam d, Raymund Schwan a, c, e, g, Grégory Gross a, c, e, g, Karine Angiol-Duprez h, Jean-Baptiste Conart b, Irving Remy b, f, Florent Bernardin e, f, Vincent Laprèvotre c, e, f, Eléa Knobloch c, g, Tiphaine Ricaud c, g, Aline Rahmna c, g, Valérie Louis-Dorr d, Thomas Schwitzer a, c, e, g, *

**A B S T R A C T**

Bipolar disorder is a lifelong condition. Today, there is a urgent need to find indicators of the disease. Specifically, they could be useful to improve the diagnosis and the early detection, the prognosis, to estimate the treatment response and to create homogeneous subgroups of patients based on similar pathophysiological mechanisms. Here, we assume that visual electrophysiology in combination with a neuropsychological assessment can give additional data to routine practice, especially to precise specific damages and pathophysiological characteristics of these patients. Visual electrophysiology is characterized by an electroretinogram and the delivery of visual evoked potentials, which measure retinal and visual cortical neuronal functioning in response to visual stimulations. This review highlights the interest of visual electrophysiology and neuropsychology performed in isolation and to present the benefits of combining these measures. We will review the results based on these measures in patients with bipolar disorders. Finally, we argue for the use of innovative techniques such as signal processing and artificial intelligence techniques for routine care and precision medicine in bipolar disorders.

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1. Introduction

Bipolar disorders (BD) affect 1–4% of the world’s population and are classified among the 10 most disabling pathologies, according to the World Health Organization (WHO) (Collins et al., 2011; World Health Organization, 2008). Today, the BD diagnosis remains clinical and the delay from the onset of the first symptoms to the initiation of appropriate treatment is approximately 10 years (Conus et al., 2008). One
brake is the lack of objective biological validation, mostly due to a scarcity of direct access to brain functioning. The need for indicators is crucial for the development of precision medicine in psychiatry. The field of precision psychiatry is designed to address these clinical problems. It leads to the development of very specific categories to better characterize the different forms of a pathology to define precise subgroups of patients and adapt care as precisely as possible. This clinical validation could be valuable in several clinical cases: diagnosis, prognosis, early detection, treatment response and for creating homogeneous subgroups of bipolar patients. For example, the first episode is often depressive and may lead to a misdiagnosis of unipolar disorder. Comorbidities such as substance use disorder can also mislead clinicians. The challenge consists in early detection of the disorder since BD can occur during adolescence. Also, it is difficult to adapt the medication treatment, where only one third of the subjects treated with lithium are responders (Rybakowski, 2011).

Among the wide choice of techniques available, we assume that visual electrophysiology is an appropriate candidate for the identification of biomarker signatures in BD (Schwizer et al., 2022b). Visual electrophysiological investigation includes an electroretinogram (ERG) examination and Cortical Visual Evoked Potentials (CVEP). The ERG is an ophthalmological examination to record the response of the layers of retinal neurons to light stimulation. CVEP are luminous visual stimuli which allow a recording of the evoked response of the visual cortex at the level of the occipital lobe (Elvásághen et al., 2012; Odom et al., 2010). Interestingly, these techniques can be combined to investigate the visual pathways, from the input of the signal to its processing by the brain. Studying these variables is relevant in isolation, but the robustness of the results may be greater when studying them in combination.

The electrophysiological measurements ERG/CVEP are disturbed in bipolar patients. The techniques enable us to study an electrical signal of the visual low-level function. Low-level vision is underpinned by basic low-level neural circuits, which process features such as contrast and motion detection. This information is then relayed to more complex neural networks (Herzog et al., 2016). Interestingly, high-level cognitive functions are also impaired in BD and there are relationships between electrophysiological abnormalities and cognitive disturbances, mainly in electroencephalography (EEG), and also recently in ERG (Bernardini et al., 2021; El-Badri et al., 2001). It is even more important to combine high and low cognitive functions given that cognitive impairments have been characterized as a core feature and a major issue in BD (Etkin et al., 2013; Keefe, 1995). These deficits are present throughout the acute phases of the disease and persist across the euthymic phase (Krabendam et al., 2005; MacQueen et al., 2001; A. Martínez-Arán et al., 2004; Torres et al., 2007). However, no clear conclusion can be drawn, mainly due to confounding factors which make it difficult to identify a specific cognitive marker in BD, as may be the case with comorbidities, treatments or clinical variables (Goodwin et al., 2008). Already integrated in the standardized care for BD, the neuropsychological assessment could be complemented by ERG and CVEP in order to identify electrophysiological indicators of the disorder and provide clinicians with critical additional and complementary information on the disorder, especially in terms of CNS damage and pathophysiological mechanisms.

In this non-systematic review, we argue that the combination of neuropsychological and electrophysiological techniques provides different and complementary cognitive information. These data could provide support for clinical decisions in daily practice. The aim of this review is to present the relevance of investigating neuropsychology and visual electrophysiology separately, as well as to discuss the relevance of combining these measures. Then, neuropsychological and visual electrophysiology results in BD will be reviewed. Next, looking to the future, we will present the possible perspectives for precision psychiatry thanks to these methods, with arguments for the implementation of artificial intelligence and deep-learning algorithms in tomorrow’s mental healthcare.

2. Method

We conducted a non-systematic review. In order to thoroughly explore the literature about visual electrophysiology and neuropsychology assessments in BD, a search for relevant articles was conducted in the Pubmed and Google Scholar databases using the following keywords: (“flash electroretinogram” OR “pattern electroretinogram” OR “retinal electrophysiological measurements” OR “electroencephalography” OR “visual evoked potentials” OR “visual electrophysiology”) AND (“bipolar disorders” OR “mood disorders”) AND (“neurocognition” OR “cognitive impairments” OR “neuropsychology”). All results up to April 1st 2022 were examined for the selection process. Relevant publications were chosen through an individual independent selection of titles by the following authors: KT, TS, IR. The articles selected had to be written in English and be related to the topic of the review. Additionally, a manual search was performed on the bibliography of each selected article.

3. Neuropsychological assessment in bipolar disorders

Cognitive impairments have been identified in BD and can therefore indicate a particular psychopathological state. Interestingly, cognitive deficits persist beyond the mood episodes and are often present during clinical stability (Krabendam et al., 2005; MacQueen et al., 2001; A. Martínez-Arán et al., 2004; Torres et al., 2007). Cognitive functions that are impaired independently of the clinical state of bipolar subjects can thus serve as indicators of the state of the disorder.

The persistence of cognitive problems often occurs despite symptomatic remission, which means that symptomatic remission is faster than functional remission (Sanchez-Moreno et al., 2018, Balanzá-Martínez et al., 2005; Purdon et al., 2000). One major issue is that neurocognitive deficits are more predictive of functional outcome than clinical variables (Duarte et al., 2016; Etkin et al., 2013; Martínez-Arán et al., 2004; Millan et al., 2012). Indeed, enduring cognitive impairments have been identified as a main cause of functional disability and can lead to a worsening of the progression of BD (Bowie et al., 2010). It should be understood that the focus needs to be on cognitive deficits in order to limit the functional impact. For example, work performance, quality of life, psychosocial functioning and self-esteem are critically reduced in BD (Bowie et al., 2006). It has also been shown that cognitive disorders are associated with poor pharmacological compliance and treatment nonadherence (Fuentes et al., 2016; Jamison and Akiskal, 1983). A crucial concern is that poor adherence to treatment can have serious consequences and can worsen the course of the illness (Etkin et al., 2013; Millan et al., 2012). For example, verbal memory performance was significantly worse in BD patients with low treatment compliance compared to those with high treatment compliance. A clearer appreciation of cognitive deficits could be key to targeting adapted treatments as quickly as possible, and hence improving clinical outcome, functional disability and quality of life for these patients (McGorry et al., 2006; Bowie et al., 2010). No clear conclusion can be drawn regarding the existence of neuropsychological subgroups in BD (Van Rheenen et al., 2017). Most studies show global rather than specific alterations of cognitive functions, and the variability mainly concerns the magnitude of the deficits (Bo et al., 2019; McTeague et al., 2016). A major challenge would be the creation of subgroups according to the severity of cognitive impairment or functional impairment. This is essential for targeting the needs of these patients and developing treatments, such as functional remediation.

However, even if the neuropsychological assessment is promising, these data remain imperfect and the conclusions of these studies are insufficient. The establishment of these subgroups will only be possible if additional parameters are included, such as electrophysiological data of the visual function. Electrophysiological data can be used alongside neuropsychological results to provide information about the neurobiological correlates regarding the disorder. In that sense, retinal and...
cortical abnormalities may be linked to the presence of cognitive impairments (Gagne et al., 2020; Bernardin et al., 2021; El-Badri et al., 2001). Combining neuropsychology with other indicators of BD could enhance the sensibility and the specificity of these variables for a better appreciation of the diagnosis and the prognosis, to evaluate the treatment response and to create BD patients’ subgroups. Indeed, investigating other kind of endophenotypes would allow a better appraisal of neurobiological mechanisms of vulnerability, and better understanding of the foundations of cognitive alterations (Nieman, 2020).

4. Anatomical and technical considerations of visual electrophysiology

The retina is formed by several types of neurons, all connected to each other via synapses and organized according to a layered architecture. The first stratum is composed of two types of photoreceptors, cones and rods, involved in high perception and colour vision and in low-light vision, respectively (McCulloch et al., 2015, Kondo et al., 2022). When a light source strikes the retina, it initiates a cascade reaction called phototransduction. The light information is then captured by the photoreceptors to be transformed into electrical information. Then, the signal is sent to the synapse and is forwarded to the bipolar cells, the second neuron layer of the retina (Hoon et al., 2014). The retina has other types of nerve cells called interneurons such as horizontal and amacrine cells, which have glial functions, like Müller’s cells (Hoon et al., 2014). The third and last layer is composed of ganglion cells, which are responsible for the interconnection between brain and retina. The axons of ganglion cells form the optic nerve and send the visual information to the cortex (Famiglietti and Kolb, 1976; Schwitzer et al., 2017).

These cells imply several neurotransmitters that can also be found in the brain, such as glutamate, dopamine, serotonin, and γ-aminobutyric acid (GABA) (Wäsle, 2004).

Retinal function can be assessed using the ERG techniques such as flash-ERG (ERG), pattern-ERG (PERG) and multifocal ERG (mFERG). The goal of these functional examinations is to explore the retinal cells’ response to light stimulations (McCulloch et al., 2015). The ERG can be combined with an electrophysiological investigation of visual cortex, known as CVEP. ERG and CVEP can therefore be performed simultaneously and share the same visual stimulations. CVEP provides post-synaptic potentials of the occipital lobe in response to visual stimulations which reflect averaged and synchronized EEG signals (Elsväshagen et al., 2012) and are relevant in exploring the integrity of the visual information along the entire visual pathway. CVEP recordings are done using multiple electrodes over the occipital surface of the scalp, connected to a recording device which ensures a high temporal resolution, on a millisecond time scale. This technique is already considered as fundamental in the fields of neurophysiology and neuroscience in the search for biomarkers and phenotypes (Sokhadze et al., 2017). Thanks to standardized protocols from the International Society for Clinical Electrophysiology of Vision (ISCEV), these examinations offer good reproducibility and reliable findings (Tan et al., 2020) (Holder et al., 2010; Marmor et al., 2009). In addition to being economical, rapid and non-invasive, ERG-mostly flash and pattern-ERG- and CVEP share the same visual stimulations, such as flashes and black-and-white reversing checkerboards, and can be performed simultaneously (Bach et al., 2013; Holder et al., 2010; Jaworska and Protzner, 2013; John et al., 2007; Odom et al., 2010). These two methods can provide neurotransmission activity data for retina and visual cortex functioning and allow understanding of anomalies in the visual pathways in BD.

5. Visual electrophysiology in bipolar disorders

The retina shares a developmental and anatomical origin with the brain (Dowling, 2012; Hoon et al., 2014). Therefore, the retina is considered as an extension of the Central Nervous System (CNS) (Hoon et al., 2014; London et al., 2013; Schwitzer et al., 2017). Disturbances of the low-level visual sensory system have been demonstrated in BD patients whether the mood state, such as a higher threshold of visual contrast and an increased contrast discrimination for low and high spatial frequencies, which possibly reveal neurophysiological abnormalities (Fernandes et al., 2019, 2017; O’Bryan et al., 2014; Oliveira et al., 2022). More precisely, O’Bryan et al. (2014) included euthymic, hypomanic, manic, depressed and mixed subjects without finding significant differences between symptomatic and euthymic BD patients. Oliveira et al. (2022) included euthymic and manic bipolar patients but there were no evaluation for the depressive symptomatology. Finally, Fernandes et al., (2017, 2019) included manic BD1 subjects. Visual electrophysiology can reflect the neurophysiological basis of neuropsychological processes in the brain. The ERG provides information about retinal function and allows assumptions to be made about the functioning of cerebral neurotransmission. Interestingly, all the pathophysiological processes are expressed in the retina, including those that are potentially involved in BD like inflammatory, immune and neurodegenerative processes. These processes, which are classically known to be of cerebral origin, give details about the pathophysiological mechanisms implicated (Ho et al., 2012; London et al., 2013). For example, these data can help with the characterization of a subtype of bipolar patient. As for the visual cortex, it can provide vital information on the continuation of early sensory processing in visual modality. Thus, it can also reflect more integrated processes, with the involvement of cognitive functions (Duncan et al., 2009; Polich, 2007). That is why it can be worthwhile coupling these measurements in order to investigate the entire visual system functioning, from the retina to the cortical regions. ERG and CVEP can distinguish where the functional visual anomalies are located since each stage of the retinal neurons can be isolated to measure its own functioning (Schwitzer et al., 2019).

Given the relevance of ERG and CVEP findings in neuropsychiatric diseases, the combination of these measures will bring robustness to the results obtained, but also increase the sensitivity and specificity of the measurements. ERG and CVEP give “low-level” information but represent objective neuronal activity. Like CVEP measurements, ERG metrics are independent of language, age or even the socio-cultural environment of individuals (Bernardin, 2019). These elements plead in favour of the high specificity and sensitivity of these two methods (Kondacs and Szabó, 1999). Substantial results have already been achieved in the investigation of the retina and visual cortex in Central Nervous System (CNS) disorders (London et al., 2013; Schwitzer et al., 2017, 2016a, 2015; Silverstein et al., 2020; Yeap et al., 2009). Visual electrophysiology is particularly suited to bipolar subjects. Previous works already highlighted ERG and CVEP abnormalities in this population (Hébert et al., 2020; Yeap et al., 2009). All of these elements lead to the conclusion that visual electrophysiology is a good model for an investigation of neurotransmission abnormalities in neuropsychiatric illnesses, in the hope of improving our understanding of their pathophysiology (Bernardin et al., 2017; Hoon et al., 2014; Lavie et al., 2014; London et al., 2013; Schwitzer et al., 2016b, 2015). Coupling visual electrophysiology will undoubtedly advance research to find strong neurobiological markers that will allow us to develop precision psychiatry. Ultimately, the clinical applications of this work are intended to highlight biomarkers of BD, which will help us to solve the current clinical problems in terms of diagnosis, differential diagnosis, early detection, prediction of response to treatment or clustering of clinical populations in homogeneous groups (McLoughlin et al., 2014).

6. Relevance of combined visual electrophysiology and neuropsychology in bipolar disorders

The previous sections of this review emphasized the relevance of neuropsychology and visual electrophysiology, investigated separately. In future clinical practice, there is clear value in combining different and complementary measures. In this section, we will discuss why it is relevant to combine several variables for more persuasive clinical
Neuropsychology and visual electrophysiology are complementary. Indeed, both assessments reflect complex neuronal responses which, on the one hand, are highly integrated with neuropsychology, and on the other, involve low-level cognitive functions in electrophysiology. Nevertheless, neuropsychological evaluations aim to study cognitive functions while electrophysiology focuses on the analysis of molecular pathophysiological mechanisms such as neurotransmission and inflammatory and immune processes (London et al., 2013). Moreover, electrophysiology is considered as a complementary examination -and not a substitute for the clinical and neuropsychological investigation- while neuropsychology can be part of the clinical practice. To carry out a neuropsychological evaluation, the motivation and the ability of the patient to mobilize their cognitive functions are necessary, while the electrophysiological examination can be done without requiring these subjects’ capacities. In addition, the subjective aspect of the cognitive evaluation can be overcome by the electrophysiology and its more objective measurements. On the one hand, ERG makes it possible to isolate an electrophysiological response devoid of any cognitive processing, because this electrophysiological measurement extracts an electrical response from the different retinal levels, in response to light stimulation that does not interfere with cerebral processes. Thus, the electrical information is not yet arrived at the cortical level. On the other hand, CVEP record the electrical response of visual cortical neuronal networks. Thus, ERG and CVEP studies are likely to indicate disturbances in neurotransmission and therefore may be linked to disturbed cognitive function (Gonthier and Hot, 2013; Schwitzer et al., 2022b). In this way, visual electrophysiology can render the electrical expression of neuropsychological disturbances and hence serve as an indicator of probable cognitive impairment. The complementarity of these two approaches also lies in the similarity of the mode of stimuli. Visual electrophysiology and neuropsychology both present stimuli in visual modality. The numerous visual stimuli used in neuropsychological tests can be seen as additional data providing more information for the investigation of visual function. All of these arguments reinforce the complementary aspect of these measurements, which provide different information but which remain nevertheless related and share similar properties.

In the literature, data suggest that correlations exist between the presence of cognitive disorders and electrophysiological abnormalities (Andersson et al., 2008). For example, Andersson showed that cognitive impairments in BD subjects were linked with EEG disturbances in the first stages of information processing, like increased latencies or reduce amplitudes of frontal waves. Although most of the results concern EEG, a recent work presents interesting findings in ERG where a link between functional retinal disturbance and poorer cognition has been found (Bernardin et al., 2021). In an ERG study, schizophrenia patients exhibiting visual hallucinations showed a difference in the rod b-wave latency on the flash ERG protocol in scotopic conditions, compared to those without visual hallucinations. These patients performed significantly worse on the visual cognition test, suggesting deficits in visual processing (Bernardin et al., 2021). (Table 1).

The preliminary results in the literature are promising, which is hopeful for the relevance of coupling of these examinations to reinforce the power of these investigations. We are probably at the beginning of investigations in this field; nevertheless, the use of coupled markers would make it possible to increase diagnosis, prognosis and therapeutic power for clinicians (Schwitzer et al., 2019). Considering that there is probably no single biomarker that can define a psychiatric disorder as defined in international classifications, it is crucial to develop alternative approaches (Fernandes et al., 2017). Coupling the different variables would be worthwhile as it would provide information on the different CNS damage and their associated pathophysiological mechanisms. The development of new technologies and artificial intelligence

Table 1
Schematic representation of the interest of studying ERG, EEG and neurocognition in neuroscience research.

| Table 1 | Schematic representation of the interest of studying ERG, EEG and neurocognition in neuroscience research. |
|---------------------------------------------|
| ![Schematic diagram](image) | |
techniques will enable the analysis of a large data sets, with the prospect of identifying biomarkers of BD. In sum, we have hopes of developing more personalized management of BD for patients and of taking a step towards precision psychiatry (Fernandes et al., 2017). The following image highlights the interconnected character of brain, retina and neurocognition and hence emphasizes the relevance of a coupled investigation of these three functions:

7. Results

7.1. Bipolar disorders and neuropsychological assessment

Cognitive impairments present throughout the acute phases of the disease and persist across the euthymic phase could represent potential trait markers of the illness (Krabbendam et al., 2005; MacQueen et al., 2001; A. Martínez-Arán et al., 2004; Torres et al., 2007). Most of the studies made during the acute phases of the illness report impairments in verbal memory, sustained attention and executive functions (EF) (Aminoff et al., 2013; Quraishi and Frangou, 2002; Robinson and Ferrier, 2006; Sweeney et al., 2000), with a specific alteration in verbal fluency which seems to be exclusive to acute moods (Kurtz and Gerratry, 2009; Martínez-Arán et al., 2004). Social cognition may also be impaired but appears to be secondary to nonsocial cognitive impairments (Bora et al., 2005; Kerr, 2003; Lahera et al., 2008). Euthymic BD usually manifest significant deficits in verbal memory, psychomotor speed, attention and executive functions (Altschuler et al., 2004; Krabbendam et al., 2005; MacQueen et al., 2001; Robinson et al., 2006; Torres et al., 2007; Ferrier et al., 1999; Thompson et al., 2005; van Gorp et al., 1998; Clark et al., 2002; Glahn et al., 2007). Nevertheless, these impairments are not shared by every euthymic BD patient (Altschuler et al., 2004; Clark et al., 2002; Ferrier et al., 1999; Thompson et al., 2005; van Gorp et al., 1998; Clark et al., 2002; Glahn et al., 2007). Nevertheless, these impairments are not shared by every euthymic BD patient (Altschuler et al., 2004; Aminoff et al., 2013; Martínez-Arán et al., 2008). According to Volkert’s study, 58.6% showed significant cognitive deficits while 41.4% had intact cognition (Volkert et al., 2015). Current clinical subgroups hardly explain cognitive heterogeneity and the interindividual variability is probably due to other factors (Bora, 2018). This may be due to a difficulty in assessing deficits, which would be linked to a lack of agreement in the literature on defining a specific deficit profile. In addition, many confounding factors may cause the results to vary, as may be the case with comorbidities, treatments, or clinical variables (Goodwin et al., 2008). Variability of cognitive impairments appears to be significantly related to clinical heterogeneity and mood state and in parallel, bipolar clinical subtype seems to influence cognitive outcome (Bora, 2018; Martínez-Arán et al., 2007). For instance, studies report more significant cognitive deficits in BDII than in BDI, especially in verbal memory, executive functions and processing speed (Bora, 2018; Bora et al., 2010; Simonsen et al., 2008; Torrent et al., 2006). The number of episodes could play a significant role: multiple episodes seem to be significantly associated with more impaired cognition, compared to a single-mood episode (Burdick et al., 2014; Kessing, 1998; Martínez-Arán et al., 2004; Robinson and Ferrier, 2006; Thompson et al., 2005; van Gorp et al., 1998). Moreover, a negative relationship has been found between neurocognition and duration of illness (Clark et al., 2002; Thompson et al., 2005; Torrent et al., 2012), the number of hospitalizations (Martínez-Arán et al., 2004; Robinson and Ferrier, 2006; Thompson et al., 2005) or even sleep disorder (Volkert et al., 2015). The most important clinical feature that may influence neuropsychological test scores in BD seems to be the presence of psychotic features (Aminoff et al., 2013; Bora, 2018; Bora et al., 2011; Glahn et al., 2007). Interestingly, BD patients with psychotic features are more impaired in verbal memory and working memory (Bora, 2018; Glahn et al., 2007; Martínez-Arán et al., 2008; Simonsen et al., 2011) but no significant association with specific cognitive deficits has been found (Bora, 2018). More than clinical symptoms, persistent cognitive deficits are one of the best predictors of functional disability (Jensen et al., 2016; Martínez-Arán et al., 2004; Torrent et al., 2012; Tse et al., 2014), and may partly explain why a high average of BD patients do not reach functional recovery after symptomatic remission (Harrow et al., 1990). Discrete cognitive subgroups are drawn rather than relying on clinical diagnosis (Bora, 2016; Burdick et al., 2014; Jensen et al., 2016; Lee et al., 2015; Lewandowski et al., 2014; Martino et al., 2008; Volkert et al., 2015). Most studies identify three subgroups: a group with normal cognitive functioning, similar to the control group, a group with selective cognitive impairment and a last group with severe cognitive disorders. A major challenge would be to identify a cognitive trait marker, which should be present both in the acute and remission phase of BD (Bora et al., 2009). The three main candidates are verbal memory, sustained attention and, to a lesser extent, executive functions, but there are no conclusive results (Aminoff et al., 2013; Bora et al., 2009; Quraishi and Frangou, 2002; Savitz et al., 2009).

In BD, the literature reports visual alterations, particularly in color discrimination (Fernandes et al., 2017). Fernandes et al. (2017) used a visual assessment involving several tasks to evaluate colour discrimination (Fernandes et al., 2017). The objective was to determine to what extent colour processing was disrupted with regard to BD and to assess the clinical and cognitive links. Existing data in the literature show a reduction and thinning of visual fibers as well as cortical thinning in bipolar subjects (Jyoo et al., 2006). In this sense, occipital thinning of the visual cortex may affect visual processing in this population. Furthermore, a link between cognitive functioning and visual tasks (such as contour grouping) has been established, showing that cognitive processing may be partially impaired by visual perception deficits (Keane et al., 2014). The authors’ hypothesis was that there is an association between visual tasks and performance on neuropsychological assessments. Deficits of the visual system may influence the performance of cognitive tests and consequently initiate cognitive impairments.

Poor colour discrimination was demonstrated in subjects with BD when compared to control subjects. Moreover, performance in visual discrimination was related to the intensity of manic symptoms assessed by the YMRS, whereas no significant differences were found between colour discrimination and the neuropsychological results. Nevertheless, the lack of differences could be explained because only colour was studied. We note that there is indeed a link between neuropsychology and the visual system. This reinforces our opinion that a complementary investigation of the functional visual system can specify and shed light on the neuropsychological profile of BD patients. Thus, questions arise about the link between BD and low cognitive function such as visual electrophysiology. All results presented here are synthesized in Table 2.

7.2. Bipolar disorders and visual electrophysiology

To date, few studies have focused on visual electrophysiology in BD but preliminary findings suggest the existence of several alterations with the disease. In her pilot study, Balogh compared the retinal function in patients with BD against healthy controls and did not find any discrepancies between them (Balogh et al., 2008). However, taking into account that only cone response was assessed, these results are likely to be due to the absence of rod examination. In contrast, Hébert et al. identified ERG discrepancies between BD subjects and healthy controls. Their study also focused on ERG differences across pathologies. On the basis of the retinal function traces, it was possible to distinguish between schizophrenia patients and BD patients. There were many similarities between these disorders, such as a reduction of cone a-wave and mixed rod-cone a- and b-wave amplitudes and an increased b-wave implicit time (Hébert et al., 2020). These results raise the question of the developmental origin of the disorder and are encouraging since they show it is possible to identify indicators for differential diagnosis.

A genetic component seems to be involved since these electrophysiological deficits were also found in high-risk offspring, who are subjects for whom there is a strong danger of evolving towards schizophrenia or BD (Rasic et al., 2014). The deficits seem to be present even before the appearance of prodromal symptoms, specifically cone response (Gagné et al., 2020). These findings back Hébert’s results, as he found reduced
### Table 2: Comprehensive results of cognitive domains affected in the BD population.

| N (BD/HC) | Phase                      | Tests                                                                 | Cognitive functions                                                                 | Anomalies observed                                                                 | References                  |
|-----------|----------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|
| 20 SZ, 40 BD, 22 HC | Euthymic                  | National Adult Reading Test (NART), California Verbal Learning Test (CVLT), Wisconsin Card Sorting Test (WCST), verbal fluency test, Rey figure test, Trail Making Test (TMT), block design, vocabulary (WAIS-R), Stroop test, Star mirror tracing task, Pursuit rotor test | premorbid IQ, verbal memory, problem solving, verbal fluency, visuospatial constructional and visual memory, mental flexibility, inhibition | SZ had a more global and more intense cognitive impairments VS BD. BD were the most impaired in EF and verbal memory. | Altshuler et al. (2004) |
| 128 BD1, 71 BD2 | Euthymic and acute        | National Adult Reading Test, CVLT-II, Bergen n-back test, Symbols (WAIS-III), Delis-Kaplan Executive Function Scale, verbal fluency test, Color-word Interference Test | Premorbid IQ, verbal learning and memory, working memory, processing speed, executive functions (EF), verbal fluency, inhibition | Important overlap between BD subgroups. Common impairments are located in verbal memory and semantic verbal fluency. | Aminoff et al. (2013) |
| 81 BD, 61 HC | Not specified             | Groningen Intelligence Test (mental rotation, word analogies, mental arithmetic), Visual/verbal learning test, Continuous Performance Task (CPT), Tapping speed test, Digit span (WAIS-III) | Intellectual functioning, verbal learning, sustained attention, selective visual control of attention, motor speed and manual dexterity, attention and working memory | BD performed worse than controls on every cognitive domain, but varied over time (2 years follow-up) except for sustained attention and motor speed which were stable over time. |                                |
| 43 BD, 30 HC | Euthymic                  | Rey Auditory Verbal Learning Test (RAVLT), verbal fluency, TMT, WCST, Stroop, CPT-II, Benton facial recognition test, eyes test, hinting task | verbal learning and memory, psychomotor speed, EF, sustained attention, social cognition (Theory of Mind (ToM), facial recognition emotions, intention recognition) | BD were impaired in several cognitive tasks, including sustained attention and theory of mind. | Bora et al. (2005) |
| Meta-analysis | Euthymic                  | /                                                                   | /                                                                                   | Verbal memory and executive functions (inhibition, set shifting) could represent potential endophenotypes in BD patients | Bora et al. (2009) |
| Review    | Euthymic                  | /                                                                   | /                                                                                   | BD type I seem to have more intense episodic memory and semantic fluency impairments compared to BD type II (mediated by psychotic features) | Bora et al. (2010) |
| Meta-analysis | Euthymic, symptomatic    | /                                                                   | Global cognition, processing speed, visual memory, attention, executive function, working memory EF, ToM | Cognitive impairment in BD is as severe as in BDII. Memory and semantic fluency are more impaired in BD1 than in BDII. 4 cognitive subgroups were identified: “neuropsychologically normal” cluster, a severe global impairment cluster | Bora et al. (2011) |
| 97 SZ or BD, 27 HC | Stable/ euthymic          | Stroop, WCST, reading the mind in the eyes test, hinting task       | /                                                                                   | /                                                                                   | (continued on next page)    |
Table 2 (continued)

| N (BD/HC) | Phase | Tests | Cognitive functions | Anomalies observed | References |
|-----------|-------|-------|---------------------|-------------------|------------|
| 136 BD, 148 HC | Euthymic | MATRICS consensus battery | Processing speed, Attention/ vigilance, working memory, Verbal learning, Visual learning, Reasoning and problem solving, Social cognition | 3 cognitive subgroups were identified: a first group with intact cognition and better social cognition than HC, an intermediate group with selective moderate impairment in memory, attention, processing speed, and social cognition, and a third group with global severe impairment in every cognitive domains | Burdick (2014) |
| 30 BD, 30 HC | Euthymic | CANTAB, NART, block design subtest (WAIS), Iowa Gambling task, CVLT | EF, sustained attention, premorbid IQ, verbal memory | BD were impaired on attention set shifting, verbal memory and sustained attention but when controlling residual symptoms, only sustained attention was still significative. | Clark et al. (2002) |
| 41 BD, 20 HC | Euthymic | / | Attention, working memory, learning and EF | BD patients performed poorly on several cognitive tests. When age and subdepressive symptoms were controlled, executive functions were still impaired. | Ferrier et al. (1999) |
| Review | Not mentioned | / | / | Cognitive impairments seem to be highly linked to psychosocial functioning | Goodwin et al. (2008) |
| 69 BD1, 35 HC | Depressed, manic, euthymic | verbal fluency, digital symbol coding (WAIS), TMT, digital span forward, identical pairs continuous performance test, spatial and object delayed response task, abstraction/inhibition/memory test, pen conditional exclusion test, CVLT, digital symbol recall, test of non-verbal intelligence, wechsler test of adult reading processing speed, EF, working memory, verbal learning and memory, attention, general intellectual functioning | Severe impairments in attention and processing speed tasks. Moderate deficits in episodic memory and EF. History of psychosis was associated with greater EF impairments. | Glahn et al. (2007) |
| 193 BD, 110 HC | Euthymic | TMT, RAVLT, letter/number sequencing subtest (WAIS-III), Digit span forward, verbal fluency processing speed, verbal fluency, working memory, verbal memory and learning, EF | Social cognition | 3 cognitive subgroups were identified: a first group without cognitive impairment (46.1%), one group with selective impairments (deficits in processing speed) (32.6%), and one last group globally impaired across verbal memory, working memory, and EF (21.2%). | Kerr (2003) |
| N (BD/HC) Phase Tests | Cognitive functions | Anomalies observed | References |
|-----------------------|---------------------|--------------------|------------|
| **20 manic, 15 depressed, 13 euthymic BD, 15 HC** | Depressed, manic, euthymic | Frith and Corcoran (1996) Theory of Mind task | Acute BD (depressed and manic) were impaired in Theory of Mind, but not in euthymic BD. | Frith and Corcoran (1996) |
| **118 MDD, 28 BD, 58 HC** | Euthymic | The Cambridge Cognitive Examination (CAMCOG), The Gottfries-Bråne-Stern (GBS) Scale, The Global Deterioration Scale (GDS), The Mini Mental State Examination (MMSE) | Number of mood episodes is associated with more impaired cognitive functions, compared to single episodes and HC. MDD and BD show no difference in the intensity of impairments. | Kessing (1998) |
| **75 BD, 48 HC** | Euthymic | Theory of Mind Advanced Test by Happe (1994), Asarnow’s Span of Apprehension Test, WCST | ToM, sustained attention, EF | Kurtz and Gerraty, (2009) |
| **61 BD, 35 SZ, 71 MDD, 63 HC** | Not clear | CANTAB, TMT A, Wechsler Test of Adult Reading, Logical Memory I & II | Premorbid IQ, psychomotor speed, verbal learning and memory, verbal fluency, sustained attention, visual learning, memory, conceptual flexibility | Lee et al. (2015) |
| **30 depressed, 34 manic/hypomanic, 44 euthymic BD, 30 HC** | Depressed, Hypomanic/ manic | WAIS vocabulary subtest, WCST, Stroop test, Controlled Oral Word Association Test, animal-naming subtests, WAIS digit subtest, TMT, CVLT, Wechsler Memory Scale-Revised (WMS-R) | Premorbid IQ, EF, attention/ concentration and mental tracking, verbal and non-verbal learning and memory | Martinez-Aran et al., (2004a) |
| **77 BD, 35 HC** | Euthymic | WAIS (vocabulary subtest, digital span subtest), WCST, Stroop test, verbal fluency, TMT, CVLT | EF, premorbid IQ, attention, verbal memory and learning | Martinez-Aran et al., (2004b) |
| **Euthymic** | / | Vocabulary subtest (WAIS), WCST, Stroop test, Controlled Oral Word Association test, digital span subtest, TMT, CVLT | Premorbid IQ, EF, attention, verbal learning and memory | Martinez-Aran et al. (2007) |
| **Euthymic** | / | Attention, psychomotor speed, verbal memory, and EF | The history of psychotic features within the course of BD influence the cognitive profile of | Martinez-Aran et al. (2008) |
| N (BD/HC) | Phase | Tests | Cognitive functions | Anomalies observed | References |
|-----------|-------|-------|---------------------|--------------------|------------|
| 41 SZ, 53 Schizoaffective, 73 BD | Stable, euthymic | TMT, Brief Visuospatial Memory test, Stroop, Hopkins Verbal Learning test, verbal fluency | Processing speed, EF, visual and verbal memory and learning, verbal fluency | 4 cognitive subgroups were identified: ‘neuropsychologically normal’ without cognitive deficits, a globally and severely impaired cluster, and two clusters of intermediate cognitive profiles. | Lewandowski et al. (2014) |
| 50 BD, 30 HC | Euthymic | Digital span subtest (WAIS), TMT, CPT, memory battery of Signoret, Boston naming test, Simple and complex motor speed, verbal fluency, WCST, facial emotion recognition test (Ekman) | Attention, verbal learning and memory, language, psychomotor speed, EF, facial emotion recognition | 3 cognitive subgroups: 38% of the sample did not have cognitive impairments, 40% had 1–2 impaired cognitive domains and 22% had 3–5. | Martino et al. (2008) |
| 51 BD, 39 HC | Euthymic | Digital span and vocabulary subtest (WAIS), verbal fluency, TMT, WCST, memory battery of Signoret, Boston naming test | Premorbid IQ, attention, EF, verbal fluency, language, verbal memory | Cognitive performance did not change during the follow-up (mean 73.21 months). Performance in verbal memory and EF were associated with the number and the length of manic episodes. | Martino et al., (2018) |
| Systematic review | Acute and euthymic | General intelligence, attention span, verbal and non-verbal memory, spatial ability, EF | Intellectual functions are preserved in BD. Verbal memory, sustained attention and inhibition are impaired in acute and euthymic phases. EF were globally impaired in symptomatic BD. | Quraishi and Frangou (2002) |
| Systematic review | Euthymic | EF and verbal learning and memory, attention and psychomotor speed | Large effect sizes for EF impairments. Moderate effect sizes for verbal memory, abstraction and set-shifting, sustained attention, inhibition and psychomotor speed. Severe cognitive deficits are associated with the number of manic episodes, length of episodes and the number of hospitalization. A low performance in verbal memory is correlated with the number of manic episodes. | Robinson et al. (2006) |
| Systematic review | Euthymic | EF, verbal fluency, verbal memory and learning, working memory, processing speed | Severe cognitive deficits are associated with the number of manic episodes, length of episodes and the number of hospitalization. A low performance in verbal memory is correlated with the number of manic episodes. | Robinson et al. (2006) |
| 25 BDI with psychotic features, 24 BDI without psychotic features, 61 HC | Euthymic, hypomanic and depressed | RAVLT, WCST, Controlled Oral Word Association Test, Stroop test, Digit span | Verbal memory and learning, verbal fluency, inhibition, working memory, EF | BD I with and without psychotic features may lie on a clinical and neuropsychological continuum mainly defined by verbal memory impairments. | Savitz et al. (2009) |
| 42 BDI, 31 BDII, 124 HC | Euthymic and low symptoms | WMS-III, CVLT-II, Digital span test (WAIS-III), Working memory-mental arithmetic test, verbal fluency, colour word interference test | Verbal learning and memory, attention, working memory, verbal fluency, EF | BD1 have greater deficits, qualitatively and quantitatively than BD2, especially verbal memory. | Simonsen et al. (2008) |
| 102 SZ, 27 Schizoaffective, 75 BD with history of psychotic | Euthymic and symptomatic | Logical Memory Test (Wechsler Memory Scale), California Verbal | Verbal learning and memory, working memory, | SZ, schizoaffective and BD with history of psychosis had poorer neuropsychological function. | Simonsen et al. (2011) |

(continued on next page)
| N (BD/HC) Phase Tests | Cognitive functions | Anomalies observed | References |
|-----------------------|---------------------|-------------------|------------|
| features, 61 BD without history of psychotic feature, 280 HC Learning Test (CVLT), Digit Symbol Test and Digital Span Test (WAIS-III), verbal fluency test, stroop test | EF, verbal fluency, processing speed | performances. History of psychosis among bipolar subjects seem to impact processing speed compared to bipolar subjects without an history of psychosis | |
| 35 BD, 58 MDD, 51 HC Manic, depressed, mixed CANTAB | verbal and spatial memory, spatial and verbal working memory, EF, problem solving | Depressed BD and MDD had impairments in verbal memory while manic and mixed BD displayed severe impairments in verbal and working memory, attention and problem solving | Sweeney et al. (2000) |
| 63 BD, 63 HC Euthymic CANTAB, TMT, vigil test, digit symbol substitution test, stroop, Tower of London, controlled oral word association test, digital backward subtest, RAVLT | Psychomotor performance, attention, EF, verbal and non-verbal memory | Significant cognitive impairments was observed in up to 42% of patients. The higher deficits are in attention, EF, memory and psychomotor speed. | Thompson et al. (2005) |
| 38 BDII, 33 BDII, 35 HC Euthymic Vocabulary subtest and DigitSpan subtest (WAIS), WCST, Stroop test, TMT, CVLT | Estimated premorbid IQ EF Attention Verbal learning and memory | Enduring cognitive impairments in BDI and in BDII have been identified despite euthymia. BDI displayed more impairments than BDII. The presence of subclinical symptoms, an early onset of illness and a poor executive performance were the best predictors of poor psychosocial functioning in BDII. | Torrent et al. (2006) |
| 68 BD, 45 HC Euthymic / | attention, psychomotor speed, verbal memory, and EF | This longitudinal study showed that attention significantly improved with time (1.5 year) and executive functions worsened, mostly due to subdepressive symptoms. No deficit on premorbid IQ. BD were significantly impaired in the cognitive domains of attention, processing speed, episodic memory, and EF. | Torrent et al. (2012) |
| Meta-analysis Euthymic | Premorbid IQ, EF, processing speed, attention, verbal memory and learning, verbal fluency, working memory | Neurocognitive performance and the course of illness better explain the favorable employment outcome than symptomatology or sociodemographic factors. BD with an alcohol dependance performed more poorly than BD without alcohol dependance in several cognitive tasks such as verbal memory and executive functions. | Torres et al. (2007) |
| Meta-analysis / / / / | / | / | Tse et al. (2014) |
| 25 BD, 22 HC Euthymic WAIS-R (vocabulary subtest, block design subtest), TMT, CVLT, Rey Osterreith Complex Figure, verbal fluency, Stroop test, WCST | Premorbid IQ, EF, verbal and visual memory and learning, verbal fluency, psychomotor speed | | Van Gorp et al., (1998) |
| 70 BD, 70 HC Euthymic Stroop test, CVLT, verbal fluency test, Test of Attentional Performance (TAP) (alertness, divided attention, working memory, shifting) | Inhibition, memory, verbal fluency, planning and problem solving, alertness, divided attention, shifting, processing speed | 41% of the BD sample did not have cognitive impairments. They performed significantly worse than HC in psychomotor speed, divided attention, working and verbal memory, word | Volkert et al. (2015) |
Euthymic BD type 1 presented a reduced amplitude of P1 compared to a focus on those recording the lateral and dorsal occipital regions. The CVEP recordings were made with a 72-electrode EEG headset, with the majority of studies concern the early visual component P1, which reflects elementary visual processing (light, contrast) (Spironelli et al., 2019). A top-down mechanism (Maekawa et al., 2013; Spironelli et al., 2019) and a putative endophenotype could be reflected by ERG anomalies. rod b-wave amplitude in young genetic at-risk subjects (Hébert et al., 2010). These findings therefore lead to some conclusions, such as the fact that a common neurodevelopmental factor is shared across these major psychiatric illnesses (Hébert et al., 2020, 2017, 2015), and a putative endophenotype could be reflected by ERG anomalies.

For the CVEP, we chose to focus only on articles mentioning the use of visual stimuli such as flash and black-and-white checkerboards, and the majority of studies concern the early visual component P1, which reflects elementary visual processing (light, contrast) (Spironelli et al., 2019). In a small study of 12 BD patients, P1 was investigated in response to isolated grey images (control condition) and drawings of animals (2 animals were 'target' animals and the rest were distractors). The CVEP recordings were made with a 72-electrode EEG headset, with a focus on those recording the lateral and dorsal occipital regions. Euthymic BD type 1 presented a reduced amplitude of P1 compared to control subjects, suggesting impairment in bottom-up visual mechanisms (Yeap et al., 2009). Other authors suggest that a decrease of P1 amplitude may also indicate selective attention deficits, according to a top-down mechanism (Maekawa et al., 2013; Spironelli et al., 2019). A more recent study by Verleger et al. (2013) including bipolar and schizophrenic subjects also demonstrated a decrease in P1 amplitude in these two populations of patients. No difference in latency was found between the groups. Although the results could not establish significance, it is likely that the component P1 is a trait indicator of vulnerability to psychosis (Verleger et al., 2013). This reflects the robustness of these three in line with previous findings which show a significant drop in the plasticity of CVEP in BD type 2 subjects compared to healthy controls (Elvsåshagen et al., 2012). Highlighting electrophysiological markers would provide an additional tool and contribute to diagnostic accuracy if subsequently integrated into regular clinical and neuropsychological practice. Visual electrophysiology added to data collection to identify biosignatures in BD may be a crucial step towards the development of precision psychiatry. All results presented here are synthetized in Tables 3 and 4.

7.3. Future directions

The previous sections of this review outlined functional abnormalities of different layers of retinal neurons, as well as the neuronal networks of the primary visual cortex (Hébert et al., 2020; Yeap et al., 2009). In particular, these disturbances are manifested by a decrease in amplitude and/or latency of the waves being studied in these examinations. At the same time, it should be noted that the presence of cognitive disorders -although heterogeneous within this population- is frequent and that discrete cognitive subgroups can be identified among bipolar subjects, depending on the intensity of the impairments (Born, 2016; Jensen et al., 2016; Lee et al., 2015; Lewandowski et al., 2014; Martino et al., 2008; Volkert et al., 2015). Links between electrophysiological alterations and cognitive disorders have once again reinforced the relevance of these investigations as a complement to increase the power of indicators and to identify the functional impairments underlying bipolar disorders (El-Badri et al., 2001; Bernardin et al., 2021).

Coupling neuropsychological and electrophysiological measurements would be an opportunity to establish certain significances that could not be determined if the measurements were taken alone. Moreover, these data would provide information on the underlying pathological processes and mechanisms. For example, indicators on the state of the disease could be identified and thus provide additional indicators to those already applied separately.

Today, it is clear that we need to move towards precision psychiatry. The results previously cited highlight the robustness of these three indicators, in an unconnected manner. The anatomical, functional and developmental similarities of the cortex and the retina lead us to believe that it is highly likely that signature biomarkers can be found. These findings could help clinicians by providing reliable and objective markers for the diagnosis of BD and may also aid in their early detection.
poor responder. Furthermore, the addition of objective indicators would facilitate the collection of new data to provide clinical decision support for BD. In this regard, the integration of visual electrophysiology into routine practice and the clinical practice (Liao et al., 2012) introducing new clinical decision rules is essential. For example, some tests have been carried out on subgroups of patients such as those comparing subjects with bipolar disorder (Redlich et al., 2014; Wollenhaupt-Aguiar et al., 2013; Volkert et al., 2015). For example, some tests have been carried out on subgroups of patients such as those comparing subjects with bipolar and unipolar depression (Redlich et al., 2014; Wollenhaupt-Aguiar et al., 2020; Yasin et al., 2021). Brain network analyses are also providers of discriminative features for depression, consisting of graph metrics extracted from brain networks estimated using EEG measurements. Several concordant studies report a higher randomness of the brain network in case of MDD when compared to the control subjects (Li et al., 2018; Shim et al., 2018). Finally, the use of Artificial Neural Networks (ANN) and deep-learning models has also emerged as a way of detecting and classifying depressive disorders based on EEG, due to their ability to identify non-linear relationships between predictive variable and complex meaningful features within raw and large data-sets, and high accuracies have been reported (Wan et al., 2020; Yasin et al., 2021). Most of the studies are carried out based on resting-state EEG, with only a few works being based on the analysis of a well-controlled and high SNR ERP event. However, they have proven to be an efficient and promising way of extracting discriminative features for depression, in particular originating from visual stimulation protocols (Mumtaz et al., 2017). For example, signal processing and machine learning tools applied on P- and PERG data provided discrimination between MDD patients and the control subjects at the inclusion (Schwitzer et al., 2022a).

When it comes to BD, and in particular to the challenging differential diagnosis between BD, MDD and schizophrenia, we are still at the very beginning of investigations. A recent study found higher clustering coefficients in the frontal lobe (Beta band) for patients suffering from schizophrenia and bipolar disorder, as well as discriminative clustering coefficients in the left inferior frontal cortex between both pathologies (Kim et al., 2020). Alpha asymmetry has been found to be an efficient discriminator of monopolar and bipolar disorders in one study (Nusslock et al., 2015), and features extracted from CVEP protocols have been identified as discriminative for MDD, bipolar disorder, and schizophrenia (Yeap et al., 2009).

Table 4

| Waves | Number of electrodes | Paradigm | Anomalies observed | Population | Phase | References |
|-------|----------------------|----------|--------------------|------------|-------|------------|
| P100  | 15                   | Visual   | Reduced VEP plasticity in BD (significantly impaired versus HC) | 26 BD, 20 HC | Euthymic | Elvsåshagen et al. (2012) |
| N100  | 128                  | Visual   | BD patients displayed early visual information processing deficits, with a reduced amplitude and latency of P1. Subsequent visual processing stages are also impaired, such as MMN and P3, and linked to higher-level cognitive functions. An increased reaction time has also been recorded. | 20 BD, 20 HC | Euthymic | Maekawa et al. (2013) |
| P100  | 38                   | Visual   | SZ exhibit a higher P1 amplitude than other groups. BD showed the lowest P1 amplitude than other groups. | 18 SZ, 20 BD, 20 MDD | Stabilized | Spironelli et al. (2019) |
| P100  | 26                   | Visual   | T1 and T2 identification rates did not substantially differ between groups. However, T1- and T2-evoked N2pc components were reduced in both patient groups. VEPs were enlarged in response to the first stimulus of the fast series in healthy participants but not in patients. T2-evoked P3 was reduced in patients with schizophrenia only. | 20 SZ, 20 BD, 21 HC | Mild psychopathological state | Verleger et al. (2013) |
| P100  | 72                   | Visual   | BD show a significant reduced P1 amplitude | 12 BD | Euthymic | Yeap et al. (2009) |

If disease-specific elements can be identified in at-risk individuals. One of the major issues for BD subjects’ healthcare is the implementation of adapted treatment. The response to lithium -the reference treatment for BD- is too low and it is now impossible to predict who will be a good or poor responder. Furthermore, the addition of objective indicators would make it possible to target the underlying pathophysiological mechanisms for the adaptation and better estimation of various drug therapy responses. Finally, the emergence of biomarkers may help with the creation of homogeneous subgroups of patients based on common features.

To this end, the search for markers is essential, using studies with large cohorts of patients on a multi-centre basis. The highly reproducible nature of electrophysiological measurements makes them very promising for advancing research into BD. There are already validated indicators for this condition, such as actimetry or electrocardiogram (ECG) (Sebela et al., 2019; Valenza et al., 2016, 2014), but there is now a need to focus on research into coupled investigations. Combined indicators are preferred to single ones to increase the relevance of the biomarker signatures and consequently improve the contribution to medical diagnosis. As previously mentioned, studies to identify indicators of BD have been carried out, with reference to control subjects but also by comparing different pathologies (Bora, 2016; Burdick et al., 2014; Hebert et al., 2020; Jensen et al., 2016; Lee et al., 2015; Lewandowski et al., 2014; Martino et al., 2008; Spironelli et al., 2019; Verleger et al., 2013; Volkert et al., 2015). For example, some tests have been carried out on subgroups of patients such as those comparing subjects with bipolar and unipolar depression (Redlich et al., 2014; Wollenhaupt-Aguiar et al., 2020). This illustrates the relevance of the coupling of variables in order to make a differential diagnosis.

It is highly probable that the ultimate goal of precision psychiatry can only be achieved with the aid of new equipment, which will provide us with more precise clinical details (Fernandes et al., 2017). The development of wearable and connected medical devices in an era of Medicine 2.0 would make these innovative practices accessible to healthcare professionals on the ground, and more widely to everyday clinical practice (Liao et al., 2012). Introducing new clinical decision support criteria will allow the expansion of these practices in specialized centres, and across the country. These innovative systems will allow the integration of visual electrophysiology into routine practice and the collection of new data to provide clinical decision support for BD. In this respect, it will be necessary to bring together a large amount of data, the integration of which would then require approaches such as artificial intelligence. The development of innovative treatment in psychiatry also implies the implementation of these additional data into signal processing and artificial intelligence tools, to enable the generation of support models for a range of important mental health concerns. The use of these techniques in our combined marker study would help to establish bio-psycho-physiological models of BD, with the aim of better understanding the processes underlying this pathology. The development of signal processing tools for the extraction of biomarkers, combined with the development of machine learning methods to build reliable decision strategies, are crucial steps towards the objectives of precision psychiatry and the design of better medication strategies. Interest in the development of such methods based on EEG recordings has been growing this last decade, in particular in the context of MDD detection and prediction (Greco et al., 2021; Wollenhaupt-Aguiar et al., 2020; Yasin et al., 2021). Brain network analyses are also providers of depression biomarkers, consisting of graph metrics extracted from brain networks estimated using EEG measurements. Several concordant studies report a higher randomness of the brain network in case of MDD when compared to the control subjects (Li et al., 2018; Shim et al., 2018). Finally, the use of Artificial Neural Networks (ANN) and deep-learning models has also emerged as a way of detecting and classifying depressive disorders based on EEG, due to their ability to identify non-linear relationship between predictive variable and complex meaningful features within raw and large data-sets, and high accuracies have been reported (Wan et al., 2020; Yasin et al., 2021). Most of the studies are carried out based on resting-state EEG, with only a few works being based on the analysis of a well-controlled and high SNR ERP event. However, they have proven to be an efficient and promising way of extracting discriminative features for depression, in particular originating from visual stimulation protocols (Mumtaz et al., 2017). For example, signal processing and machine learning tools applied on PERG data provided discrimination between MDD patients and the control subjects at the inclusion (Schwitzer et al., 2022a).
demonstrated to be helpful in classifying BD and schizophrenia (Ali-mardani et al., 2018). Very few works based on ANN could be found for BD detection and discrimination (Lei et al., 2022), partly due to the lack of sufficient amounts of available labelled data (Yasin et al., 2021).

The development of such tools on ERG for the detection of depressive states still remains to be explored. This field of investigation is currently based on the analysis of well-defined waves latency and amplitudes (Bubl et al., 2010; Schwindt et al., 2022a, 2015). We can expect more from advanced analysis of such signals, as demonstrated in Schwindt et al. (2022b) for the discrimination between MDD and healthy controls. In particular, we emphasize the fact that, beyond well-known wave characteristics picked up at specific instants on the signal, analysing the signal as a whole can provide additional information not only for differentiating between normality and abnormality, but also for patient follow-up throughout the period of treatment/medication. For example, signal processing and machine learning tools applied on PERG data reflected the efficacy of the treatment at the follow-up appointment at week 12 after treatment (Schwindt et al., 2022a). These data suggest a normalization of the Mahalanobis distance between depressed and healthy people.

A major challenge is the development of methods for patient follow-up and medication prediction. A wide spectrum of EEG-based features have proven to hold valuable information for medication prediction (Mumtaz et al., 2017; Olbrich and Conrad, 2016), ranging from band power analysis, connectivity measures or event-related potentials to cite just a few. However, these findings still need to be consolidated for their effective clinical application (Widge et al., 2019). The main limitations preventing us from drawing decisive conclusions in this field are very certainly the lack of extended databases for various pathologies and conditions, recorded within a uniform setup so that the methods can be reproduced in clinical routine. A challenge lies in the acquisition of large enough sample sizes to address specific predictors related to cofactors such as gender, age and drug class, but also to overcome the lack of standardized and well-controlled conditions during acquisition. Most of the studies are carried out in a resting state, and the analysis would benefit from the well-controlled conditions brought about, for example, by visual stimulation protocols. The combination of ERG and EEG data in this context is of high interest, in particular for the characterization of changes in the organization of the visual pathway network, holding primary functions in the retina to more complex processing functions in visual regions of the anterior cortex. Future studies are required, with the recruitment of numerous patients, across different populations and in a multi-centre manner. In the long term, we hope to highlight markers that will allow us to develop precision psychiatry. These data will be crucial in the development of precision psychiatry and will be essential for developing clinical decision support models.

8. Conclusion

In brief, this review of the literature provides evidence that BD subjects have impaired visual perception, electroretinography, and response to visual evoked potentials in the visual cortex. The difficulty in finding specific biomarkers for a particular neuropsychiatric pathology leads us to believe that these measures need to be coupled to improve the power of techniques for exploring CNS disorders. Combined measurements of ERG and CVEP may provide information on the early and later localization of functional deficits in the visual system (Schwindt et al., 2019). In addition, electrophysiology could help to better understand neuropsychological correlates. There is huge potential for improving the diagnosis and the prognostic, evaluating the pharmacological treatments response and finding neurocognitive phenotypes. For our work, among the existing indicators, we assume that visual electrophysiology and neuropsychology are relevant candidates for the future. Coupling these variables with one another, as well as combining them with other measurements, would help increase the power of the markers. This would be valuable for clinical applications, to reduce the problems currently encountered in clinics in terms of diagnosis, differential diagnosis, early detection, evaluation of the response to treatment, or for the creation of homogeneous subgroups of bipolar patients, which could undoubtedly improve patients’ lives.

Author contributions

All the authors contributed to write the manuscript, concurred with the submission and have approved the final manuscript.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest.

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