Journal of Affective Disorders

Electrodermal activity in bipolar disorder: differences between mood episodes and clinical remission using a wearable device in a real-world clinical setting.

--Manuscript Draft--

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Abstract:	Background Bipolar disorder (BD) lacks objective measures for illness activity and treatment response. Electrodermal activity (EDA) is a quantitative measure of autonomic function, which is altered in manic and depressive episodes. We aimed to explore differences in EDA (1) inter-individually: between patients with BD on acute mood episodes, euthymic states and healthy controls (HC), and (2) intra-individually: longitudinally within patients during acute mood episodes of BD and after remission. Methods A longitudinal observational study. EDA was recorded in BD during acute manic and

	depressive episodes and at clinical remission. Euthymic BD patients and HC were recorded during a single session. We compared EDA parameters derived from the tonic (mean EDA, mEDA) and phasic components (EDA peaks per minute, pmEDA, and EDA peaks mean amplitude, pmaEDA). Inter- and intra-individual comparisons were computed respectively with ANOVA and paired T-tests. Results 49 patients with BD (15 manic, 9 depressed, and 25 euthymic), and 19 HC were included. Patients with bipolar depression showed significantly reduced mEDA ($p=0.003$) and pmEDA ($p=0.001$), which increased to levels similar to euthymia or HC after clinical remission (mEDA, $p=0.011$; pmEDA, $p<0.001$; pmaEDA, $p<0.001$). Manic patients showed no differences compared to euthymic patients and HCs, but a significant reduction of EDA parameters after clinical remission (mEDA, $p=0.035$; pmEDA, $p=0.004$). Limitations Limited sample size, high inter-individual variability, limited comparability and non-adjustment for medication. Conclusion EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments in mania and bipolar depression.
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Opposed Reviewers:	
Response to Reviewers:	See "response to reviewers" file.

10th July 2023

Prof. P. Brambilla and Prof. J.C. Soares,
Editors-in-Chief
Journal of Affective Disorders

Dear Prof. P. Brambilla and Prof. J.C. Soares,

Please find enclosed our manuscript titled "Electrodermal activity in bipolar disorder: differences between mood episodes and clinical remission using a wearable device in a real-world clinical setting" to be considered for publication as a *Research Paper* in *Journal of Affective Disorders.*

We conducted a longitudinal observational study to explore Electrodermal activity (EDA) (1) inter-individually: between patients with bipolar disorder on acute mood episodes, euthymic states and healthy controls, and (2) intra-individually: longitudinally within patients during acute mood episodes of bipolar disorder and after clinical remission.

We found that patients with bipolar depression showed significantly reduced EDA, which was normalized after clinical remission. Moreover, patients with manic episodes showed a significant reduction of EDA after clinical remission.

Our results suggest that EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments in mania and bipolar depression.

We declare that this manuscript is original, has not been submitted or published before and is not currently being considered for publication elsewhere.

We confirm that all listed authors have contributed significantly to the manuscript, that the manuscript has been read and approved by all named authors, and that there are no other persons who satisfied the criteria for authorship but are not listed.

My co-authors and I hope that this paper will be of interest and look forward to hearing from you in due course.

Yours sincerely,

Dr. Gerard Anmella, M.D., Ph.D.

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16th October 2023

Prof. P. Brambilla and Prof. J.C. Soares,
Editors-in-Chief
Journal of Affective Disorders

Dear Prof. P. Brambilla and Prof. J.C. Soares,

Thank you very much for your consideration of our manuscript titled "Electrodermal activity in bipolar disorder: differences between mood episodes and clinical remission using a wearable device in a real-world clinical setting" and your request for a revised version. We have taken into careful consideration all the reviewers' comments which can be found copied and pasted below. We have thoroughly addressed each one individually, and made modifications in the manuscript following reviewers' suggestions which have helped us to significantly improve the manuscript.

For ease of reading, you will find the reviewers' comments followed by our responses and changes in the article.

Reviewer 1:

To better understand bipolar disorder it is important to study changes in physiological parameters in naturalistic settings. Activation is central to understand bipolar pathophysiology and advances in sensor technology has now made it possible to follow changes in sympathetic activity over time. The present study is good example of this. This is a well conducted study. It is not easy to obtain samples such as presented here. The authors have given a good overview of the literature and the results are adequately discussed, including limitations.

RESPONSE: We thank the reviewer for the comprehensive review of our article and for the helpful comments. We will try to provide our best answers to each of the points mentioned.

I have two questions: It would be interesting to know how the criteria for detecting artifacts in the recordings and how much of the recordings were discarded because of this. Was the length of discarded segments different between the groups?

RESPONSE: We thank the reviewer for mentioning this important point. We agree with the reviewer that artifact detection is key, especially when considering ambulatory measurements of EDA, and that methods should be clear for other groups to replicate. We added the requested information in the method section, as follows: "Data collected by the wearables were processed with the "Wearables" which is an R package designed to pre-process, detect artifacts, and extract features in data from the Empatica E4 (de Looff et al., 2022). Artifact detection in EDA signal is performed after pre-processing following the algorithm developed by Taylor et al. (Taylor et al., 2015). In short, several features are extracted from the EDA signal, which is put into an algorithm that classifies for each segment of 5 seconds, whether this segment contains an artifact. The algorithm is a support vector machine pre-trained on expert data. Calculations are performed on the segment and one-second and half-a-second wavelet decompositions of the measurements. The pre-training also determined which of the features are used in the support vector machine algorithm. The algorithm has two settings, binary classification (artifact and no artifact) and ternary classification (artifact, unclear, and no artifact).".

Moreover, as requested by the reviewer, we added quantitative information on artifact detection from our EDA data and compared differences between groups. This can be found at the results section, as follows: "For T0, the median percentage of data per recording session dropped from further analysis due to artifact detection was 31.89; interquartile range (IQR) 28.05 for mania, 10.72; IQR 72.46 for depression, 13.23; IQR 17.83 for euthymia, and 14.50; IQR 14.09 for HC. There were no significant differences on discarded segments due to artifact detection between groups (H (3) = 7.06, p = 0.07). For T1, the median percentage of data per recording session dropped from further analysis due to artifact detection was 12.40; IQR 17.53 for mania, and 17.36; IQR 57.60 for depression. There were no significant differences on discarded segments due to artifact detection between groups (U = 47.0, p = 0.22).".

Chronobiology is important in psychiatry - was there any difference in diurnal EDA activity between groups?

RESPONSE: We thank the reviewer for bringing this up. In fact, we already mentioned this in the limitations section, as follows "Furthermore, analyses were performed without considering sleep versus wake times, in which sympathetic activity (and consequently EDA parameters) have a huge variability and may have influenced the results.". This is an important limitation that we are aware of, however the study aimed to perform an ambulatory measurement of EDA without interfering with the patients' routines or requesting them to annotate sleep hours or other potentially relevant information. Since we did not have this information and the package used for the analyses was not able to detect sleep, we could not perform the precise analyses in the current study. However, in further analyses we are working to implement automated sleep detection based primary on accelerometry data collected by the E4 wearables. This will allow to perform separate analyses for sleep and wake times. We have included this explanation in the limitations section, as follows: "Considering the expected marked differences in EDA between wake and sleep times, further analyses of the current work will include the respective sub-analyses of EDA between sleep and wake times using automated sleep detection methods.".

Reviewer 2:

The article "Electrodermal activity in bipolar disorder: differences between mood episodes and clinical remission using a wearable device in a real-world clinical setting" reports on the important topic of objective indicators of clinical change in mood disorders. The manuscript is very well written and situated succinctly, yet effectively the study, in the existing literature. The method is generally adequately reported to allow replication, and the limitations of the research are overall very well described and discussed. However, the discussion of the results should be nuanced relative to the findings in the "manic" sub-group. Specifically, there are no significant differences at baseline between the "manic" sub-group and the remaining groups, therefore the decrease cannot be interpreted as an indicator of response. The authors thus need to address this, and related points as follows:

RESPONSE: We thank the reviewer for a comprehensive review of our article and for the helpful comments. We will try to provide our best answers to each of the points mentioned.

1. Abstract: within the limitations, the lack of elicitation is not really a limitation, given the context, but all the individual variability factors appearing in the first lines of page 24 are, with the medication being only one of them. The authors should revise this along the lines of "important inter-individual variability in physiological factors".

RESPONSE: We thank the reviewer for bringing this up. We agree that there is important inter-individual variability in physiological factors, including the EDA parameters measured and compared in the current study, and this is a limitation. We apologize if this was not clear enough in the abstract section. We also agree with the reviewer that "lack of elicitation" is not a limitation per se. However this hinders comparability to previous studies. We amended all this accordingly in the abstract section, as follows: "**Limitations**: Limited sample size, high inter-individual variability in~~lack of~~ EDA parameters, limited comparability to previous studies ~~elicitation~~ and non-adjustment for medication."

2. Results - Table 1: the demographic and medical comorbidity variables should be reported by subgroups and not as a unified bipolar group, and then appropriate tests should be used for comparisons.

RESPONSE: We thank the reviewer for pointing this out. We have added the required sub-analyses in Table 2, as follows: "Sociodemographic and clinical information of both groups is reported in **Table 1**, and is detailed according to each mood episode group in **Table 2**."."The BD and HC population were comparable in terms of age, sex, and medical comorbidities (**Table 1**). There were also no significant differences between mood episode groups (**Table 2**).".

As the comparisons for age, sex, and medical comorbidities between mood episodes subgroups were non-significant this has not influenced the discussion, and points toward less biased comparability between those subgroups (Inter-subject comparisons).

3. Discussion - the marginally significant decrease in the manic group might have many explanations given the high interindividual variability in the variables of interest as the authors themselves describe in detail in the limitations. The results do not support a detection of response, given that the group is not different relative to others. The results support only the conclusion for the "depression" group. To be nuanced/revised in that respect:
a. Discussion end 1st paragraph: should be "depressive" not affective and "digital biomarker" should be limited to "depressive episodes", i.e., remove manic;
b. P.22, 2nd paragraph, starting with "Moreover," should be nuanced, or better deleted, as the results cannot be interpreted as a normalisation, given that those parameters were normal to start with.
c. P. 22, last paragraph, remove "and manic", and limit to depressive
d. P.23 2nd line, remove "mania"
e. Abstract, remove "mania"

RESPONSE: We thank the reviewer for mentioning this important point. Indeed, when manic patients are compared to other subgroups (Intra-individual comparisons), EDA parameters are higher compared to depressed patients, but no significant differences are present when compared to healthy controls or euthymic patients (**Figure 1**). However, when manic patients are compared to themselves after achieving clinical remission (Intra-individual comparisons), there is a clear reduction in EDA parameters (**Figure 2**). Even we acknowledge the interindividual variability of EDA parameters, as discussed above, this would mostly affect inter-individual comparisons, and would likely be less

marked when comparing an individual with themselves. This has been further clarified to avoid misunderstanding in several parts of the manuscript:

Abstract: “Manic patients showed no differences compared to euthymic patients and HCs, but a significant reduction of tonic and phasic EDA parameters after clinical remission (mEDA, p=0.035; pmEDA, p=0.004).”.

Highlights: “EDA is reduced during bipolar depression and ~~normalized~~ increases after remission.”.

Discussion: “Our results may be interpreted as the ~~normalization~~ reduction of a probably excessive sympathetic activity during manic episodes (Swann et al., 1991).”.

We would like to reiterate your kind reconsideration of this submission and the detailed review provided by external reviewers, which have resulted in a much-improved version of the original manuscript. We hope that the new version will now be suitable for publication in *Journal of Affective Disorders*.

Yours sincerely,

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Highlights

- EDA is reduced during bipolar depression and ~~normalized~~ increases after remission.
- Ecological monitoring of EDA might allow early detection of depressive symptoms.
- Electrodermal activity (EDA) ~~increases~~ is reduced after remission of a manic episode.
- EDA might aid to asses early response to treatment in mania and bipolar depression.

Abstract

Background: Bipolar disorder (BD) lacks objective measures for illness activity and treatment response. Electrodermal activity (EDA) is a quantitative measure of autonomic function, which is altered in manic and depressive episodes. We aimed to explore differences in EDA (1) inter-individually: between patients with BD on acute mood episodes, euthymic states and healthy controls (HC), and (2) intra-individually: longitudinally within patients during acute mood episodes of BD and after clinical remission.

Methods: A longitudinal observational study. EDA was recorded using a research-grade wearable in patients with BD during acute manic and depressive episodes and at clinical remission. Euthymic BD patients and HC were recorded during a single session. We compared EDA parameters derived from the tonic (mean EDA, mEDA) and phasic components (EDA peaks per minute, pmEDA, and EDA peaks mean amplitude, pmaEDA). Inter- and intra-individual comparisons were computed respectively with ANOVA and paired T-tests.

Results: 49 patients with BD (15 manic, 9 depressed, and 25 euthymic), and 19 HC were included. Patients with bipolar depression showed significantly reduced mEDA ($p=0.003$) and pmEDA ($p=0.001$), which increased to levels similar to euthymia or HC after clinical remission (mEDA, $p=0.011$; pmEDA, $p<0.001$; pmaEDA, $p<0.001$). Manic patients showed no differences compared to euthymic patients and HCs, but a significant reduction of tonic and phasic EDA parameters after clinical remission (mEDA, $p=0.035$; pmEDA, $p=0.004$).

Limitations: Limited sample size, high inter-individual variability of~~lack of~~ EDA parameters, limited comparability to previous studies ~~elicitation~~ and non-adjustment for medication.

Conclusion: EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments in mania and bipolar depression.

Keywords: Electrodermal activity, bipolar disorder, depression, mania, biomarker, treatment response.

Conflict of interests

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, Rovi, Casen Recordati, and Angelini, with no financial or other relationship relevant to the subject of this article.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag, and Lundbeck. IG has received grants and served as consultant, advisor or CME speaker for the following identities: Angelini, Casen Recordati, Ferrer, Janssen Cilag, and Lundbeck, Lundbeck-Otsuka, Luye, SEI Healthcare.

IG has received grants and served as consultant, advisor or CME speaker for the following identities: Angelini, Casen Recordati, Ferrer, Janssen Cilag, and Lundbeck, Lundbeck-Otsuka, Luye, SEI Healthcare.

AGP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Casen Recordati, LCN and Angelini.

GF has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck; GF's work is supported by a fellowship from "La Caixa" Foundation (ID 100010434 fellowship code LCF/BQ/DR21/11880019).

AHY has received honoraria for lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders.

EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work;

DHM has received CME-related honoraria and served as consultant for Abbott, Angelini, Ethypharm Digital Therapy and Janssen-Cilag.

All authors report no financial or other relationship relevant to the subject of this article.

Authors' Contributions

GA and DH-M were responsible for study planning, project conception, and coordination. A Mas, MS, CV-P, MV, IP, A Benabarre, IG, AG-P, MG, A Bastidas, and IA were responsible for recruitment. DH-M, A Mas, PdL, FC, BML, MDP, VO, and GF were responsible for data analysis. GA and DH-M were responsible for manuscript preparation. All authors revised the final manuscript.

Role of the Funding Source

This project was funded by the ISCIII (FIS PI21/00340, TIMEBASE Study), cofunded by the Euopean Union, as well as a Baszucki Brain Research Fund grant (PI046998) from the Milken Foundation. The ISCIII or the Milken Foundation had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Data Availability

The data supporting the findings of this study are available upon request from the corresponding author.

Acknowledgments

The authors acknowledge the contribution of all the participants and collaborators of this study.

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GA is supported by a Rio Hortega 2021 grant (CM21/00017) from the Spanish Ministry of Health financed by the Instituto de Salud Carlos III (ISCIII) and cofinanced by Fondo Social Europeo Plus (FSE+).

A Mas and **CVP** are supported by a contract funded by MCIN/AEI/TED2021-131999BI00 Strategic Projects Oriented to the Ecological Transition and the Digital Transition 2021 and by the "European Union NextGenerationEU/PRTR".

MS is supported by a grant from the Baszucki Brain Research Fund from the Milken Foundation.

IG thanks the support of the Spanish Ministry of Science and Innovation (PI19/00954) integrated into the Plan Nacional de I+D+I and cofinanced by the ISCIII-Subdirección General de Evaluación y el Fondos Europeos de la Unión Europea (FEDER, FSE, Next Generation EU/Plan de Recuperación Transformación y Resiliencia_PRTR); the ISCIII; the CIBER of Mental Health (CIBERSAM); and the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), Centres de Recerca de Catalunya (CERCA) Programme or Generalitat de Catalunya as well as the Fundació Clínic per la Recerca Biomèdica (Pons Bartran 2022-FRCB_PB1_2022).

AGP is supported by a Rio Hortega 2021 grant (CM21/00094) from the Spanish Ministry of Health financed by ISCIII and cofinanced by Fondo Social Europeo Plus (FSE+).

GF received the support of a fellowship from "La Caixa" Foundation (ID 100010434 - fellowship code LCF/BQ/DR21/11880019).

FC and **BML** are supported by the United Kingdom Research and Innovation (grant EP/S02431X/1), UK Research and Innovation (UKRI) Centre for Doctoral Training in Biomedical AI at the University of Edinburgh, School of Informatics.

EV thanks the support of the Spanish Ministry of Science and Innovation (PI18/00805, PI21/00787) integrated into the Plan Nacional de I + D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), the CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357, and the European Union Horizon 2020 research and innovation program (EU.3.1.1. Understanding health, wellbeing and disease: Grant No 754907 and EU.3.1.3. Treating and managing disease: Grant No 945151).

Electrodermal activity in bipolar disorder: differences between mood episodes and clinical remission using a wearable device in a real-world clinical setting.

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Abstract

Background: Bipolar disorder (BD) lacks objective measures for illness activity and treatment response. Electrodermal activity (EDA) is a quantitative measure of autonomic function, which is altered in manic and depressive episodes. We aimed to explore differences in EDA (1) inter-individually: between patients with BD on acute mood episodes, euthymic states and healthy controls (HC), and (2) intra-individually: longitudinally within patients during acute mood episodes of BD and after clinical remission.

Methods: A longitudinal observational study. EDA was recorded using a research-grade wearable in patients with BD during acute manic and depressive episodes and at clinical remission. Euthymic BD patients and HC were recorded during a single session. We compared EDA parameters derived from the tonic (mean EDA, mEDA) and phasic components (EDA peaks per minute, pmEDA, and EDA peaks mean amplitude, pmaEDA). Inter- and intra-individual comparisons were computed respectively with ANOVA and paired T-tests.

Results: 49 patients with BD (15 manic, 9 depressed, and 25 euthymic), and 19 HC were included. Patients with bipolar depression showed significantly reduced mEDA ($p=0.003$) and pmEDA ($p=0.001$), which increased to levels similar to euthymia or HC after clinical remission (mEDA, $p=0.011$; pmEDA, $p<0.001$; pmaEDA, $p<0.001$). Manic patients showed no differences compared to euthymic patients and HCs, but a significant reduction of tonic and phasic EDA parameters after clinical remission (mEDA, $p=0.035$; pmEDA, $p=0.004$).

Limitations: Limited sample size, high inter-individual variability of~~lack of~~ EDA parameters, limited comparability to previous studies ~~elicitation~~ and non-adjustment for medication.

Conclusion: EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments in mania and bipolar depression.

Keywords: Electrodermal activity, bipolar disorder, depression, mania, biomarker, treatment response.

Word count: 3,460~~171~~ words

Highlights

- EDA is reduced during bipolar depression and ~~normalized~~ increases after remission.
- Ecological monitoring of EDA might allow early detection of depressive symptoms.
- Electrodermal activity (EDA) ~~increases~~ is reduced after remission of a manic episode.
- EDA might aid to asses early response to treatment in mania and bipolar depression.

Introduction

Bipolar disorder (BD) is a chronic mental health condition characterized by pathological mood states encompassing depressive and manic episodes. Beyond mood episodes and despite optimal treatment, BD can still have enduring detrimental long-term consequences on individual's functionality, quality of life, cognition, and morbimortality (Vieta et al., 2018).

Assessments for diagnosis, illnesss activity (e.g. mood episodes, symptom severity), and treatment response in BD are still based on subjective reports from clinical interviews, questionnaires, and standardized scales (Miller et al., 2009). Despite the intensive research in the field to find specific and objective biomarkers, none of the few promising biomarkers identified has been implemented in real-world clinical practice so far (Carvalho et al., 2020).

Recent advances in wearable technologies has allowed to ubiquitously collect in real-world, ecological settings a multitude of physiological signals, including heart rate, temperature, blood pressure, and also electrodermal activity (EDA), which was previously restricted to laboratory or hospital settings (Hsin et al., 2018). Compared to traditional methods for measuring the previous physiological data, digital devices allow for continuous, longitudinal, granular, unobtrusive, and usually cost-efficient measurements (Babrak et al., 2019). Over the last decade, there has been increasing interest in exploring the association of physiological digital data with behavioural alterations in psychiatric disorders. The associations between these digital data and disease-related outcomes have been denominated digital biomarkers (Vasudevan et al., 2022).

One physiological signal that has been studied for more than a century is EDA, also known as galvanic skin response. EDA has been investigated as a potential biomarker in mood disorders in numerous laboratory studies and is seen as a cost-effective method to assess the arousal of the sympathetic nervous autonomous system, and has been a popular index to study the significance and intensity of various laboratory induced (emotional) stimuli (Boucsein et al., 2012; Johnson and Picard, 2020; Sarchiapone et al., 2018; van Lier et al., 2020). The EDA signal is an electrical manifestation of the sympathetic innervation of the sweat glands. Emotion-evoked increased sweating augments the electrical conductance of the skin. Therefore, EDA is believed to represent a quantitative measure of autonomic function and an objective assessment of cognitive arousal (Setz et al., 2010). EDA makes it theoretically possible to estimate the

time and amplitude of stimuli generated from control centres in the brain by interpreting the manifestation of their arrival at the skin level, which is observable in the EDA signal. In sum, EDA is a the result of different processes in the skin and seems to be solely innervated by the sympathetic nervous system (Posada-Quintero and Chon, 2020).

EDA can be decomposed into tonic and phasic components: tonic activity varies relatively slowly and is also referred to as skin conductance level (SCL), while phasic activity varies rapidly in response to stimuli such as stress and is also referred to as the skin conductance response (SCR). SCR is characterized by a rapid incline to a peak and then a slower decline back to the individual's SCL (**Figure 1**) (Boucsein et al., 2012). Both are strongly and dynamically linked to the sympathetic nervous autonomous system via sweating regulation controlled by brain regions implicated in emotion, attention, and cognition such as the prefrontal cortex, amygdala, hippocampus, and cingulate cortex (Critchley, 2002).

[Figure 1 goes here]

Coincidentally, meta-analyses of functional magnetic resonance imaging (fMRI) studies have revealed dysfunction of these same areas in patients with BD (Chen et al., 2011). In addition, several studies showed EDA hypo-reactivity in depression and suicidal behaviour (Sarchiapone et al., 2018). To date, only a few studies have explored EDA's potential in differentiating mood episodes or assessing clinical response in BD (Greco et al., 2014). Furthermore, to our knowledge, no studies have been yet performed using a wearable device in an ecological setting on BD patients. Considering the recent possibility of continuously monitoring EDA with unobtrusive wearables, we aimed to explore differences in EDA (1) inter-individually: between patients with BD on acute mood episodes or euthymic states and healthy controls (HC), and (2) intra-individually: longitudinally within patients during an acute mood episode of BD and after clinical remission in a real-world clinical setting.

Methods

This is a longitudinal observational study including patients with BD on acute manic and depressive episodes or euthymic phases, according to DSM-5 criteria (APA, 2013). Patients were recruited from various clinical settings including inpatient, home-treatment and outpatient units from the Bipolar and Depressive Disorders Unit at the Hospital Clínic de Barcelona. Further details on inclusion/exclusion criteria have been reported elsewhere (Anmella et al., 2023). Participants needed to provide written informed consent. In patients on acute episodes, their capacity to provide informed consent was assessed at inclusion and re-assessed after remission.

Sociodemographic and clinical variables (i.e., current and previous diagnosis, duration of illness, psychiatric and medical comorbidities) were collected. Manic and depressive symptoms were assessed respectively using standardized psychometric scales: the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978) and the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafafila, 1988). HC were recruited from a convenience sample of researchers and relatives.

EDA was recorded using a research-grade wearable (Empatica E4 (Empatica, 2022)) in patients with BD during acute manic and depressive episodes and at clinical remission, defined as standardized clinical scores ≤7 at YMRS and HDRS (i.e., symptoms absent or nearly absent) (Tohen et al., 2009). Euthymic BD patients and HC were recorded during a single session. All sessions lasted approximately 48 hours, due to limited battery life of the device.

We compared continuous registers of EDA parameters from the tonic (i.e., mean EDA, as proxy for the SCL) and phasic components (i.e., EDA peaks per minute, EDA peaks mean amplitude, extracted from the SCR) in patients with BD (1) inter-individually during acute manic and depressive episodes, euthymia, and healthy controls (HC), and (2) intra-individually during acute manic and depressive episodes, and after remission of the episode.

Data collected by the wearables were processed with the "Wearables" which is an R package designed to pre-process, detect artifacts, and extract features in data from the Empatica E4 (de Looff et al., 2022). Artifact detection in EDA signal is performed after pre-processing following the algorithm developed by

Taylor et al. (Taylor et al., 2015). In short, several features are extracted from the EDA signal, which is put into an algorithm that classifies for each segment of 5 seconds, whether this segment contains an artifact. The algorithm is a support vector machine pre-trained on expert data. Calculations are performed on the segment and one-second and half-a-second wavelet decompositions of the measurements. The pre-training also determined which of the features are used in the support vector machine algorithm. The algorithm has two settings, binary classification (artifact and no artifact) and ternary classification (artifact, unclear, and no artifact). The "Wearables" package can be used in combination with a user interface called the E4 dashboard. Researchers can visualize the physiological signals and have several algorithms available to detect artifacts in the raw physiological signals, and extract relevant features for analysis. A *batch* analysis function is available to extract relevant features for all the physiological signals that are available from the Empatica E4 (acceleration, blood volume pulse, heart rate, interbeat-interval, EDA, and temperature). For the current study, the resulting relevant EDA features were extracted for each subject´s session, specifically mean EDA (mEDA), EDA peaks per minute (pmEDA) and EDA peaks mean amplitude (pmaEDA). Statistical analyses were computed with SPSS 28 (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Normality of EDA parameters were assessed using the Shapiro-Wilk test. Accordingly, inter- and intra-individual comparisons were computed respectively with ANOVA with Tukey's post-hoc test for multiple comparisons, and paired T-tests. Subsequently, significant results were controlled for covariates that could affect dependent variables such as age, sex and medical comorbidity with an ANCOVA and ANCOVA for repeated measures.

Results

A total of 49 subjects with the diagnosis of BD (15 manic, 9 depressed, and 25 euthymic) and 19 HCs were recruited and included in the analyses. Sociodemographic and clinical information of both groups is reported in **Table 1**, and is detailed according to each mood episode group in **Table 2**. Clinical information of patients with BD, including the type of BD, substance use disorder (SUD), illness duration, presence of psychotic features during an episode, and affective symptoms' scores during acute mood episodes and after remission are detailed in **Table 2**.

[Table 1 goes here]

[Table 2 goes here]

The BD and HC population were comparable in terms of age, sex, and medical comorbidities (**Table 1**). There were also no significant differences between mood episode groups (**Table 2**). Most patients had BD type 1 and more than 75% did not have history of SUD. Only manic patients presented with psychotic symptoms during acute episodes (60%). Duration of illness was shorter ($F=3.23$, $p=0.049$) for patients with mania (6.6±7.7 years) compared to patients with depression (17.1±11.3 years) and euthymia(13.8±8.9 years). Mean YMRS for patients with manic episodes was 26.8±4.7 at T0, with a reduction to 3.7±4.3 at T1. Mean HDRS for patients with bipolar depression was 18.4±4.7 at T0, with a reduction to 3.9±2.1 at T1 (**Table 2**). A total of 3,227 hours (approximately 134 days) were recorded at T0 for the whole sample averaging 47.5±6.9 hours per session (SD=7.1), while 1,124 hours (approximately 47 days) were recorded at T1 follow-ups of BD patients with an average of 46.8±7.7 hours per session. For T0, the median percentage of data per recording session dropped from further analysis due to artifact detection was 31.89; interquartile range (IQR) 28.05 for mania, 10.72; IQR 72.46 for depression, 13.23; IQR 17.83 for euthymia, and 14.50; IQR 14.09 for HC. There were no significant differences on discarded segments due to artifact detection between groups ($H(3) = 7.06$, $p = 0.07$). For T1, the median percentage of data per recording session dropped from further analysis due to artifact detection was 12.40; IQR 17.53 for mania, and 17.36; IQR 57.60 for depression. There were no significant differences on discarded segments due to artifact detection between groups ($U = 47.0$, $p = 0.22$). The explored EDA variables (mEDA, pmEDA, pmaEDA) followed a normal distribution according to the Shapiro-Wilk test ($p > 0.20$).

Inter-subject comparisons of EDA parameters are shown in **Figure 2**. Patients with bipolar depression (0.43±0.22) had a statistically significantly lower mEDA ($F(3, 67) = 5.860$, $p=0.003$) when compared to mania (2.05±1.16, $p=0.003$), euthymia (1.92±1.38, $p=0.004$), and HCs (1.76±0.62, $p=0.016$). Similarly, pmEDA were significantly lower ($F(3, 67) = 8.062$, $p=0.001$) in patients with bipolar depression (1.01±0.72) when compared to mania (2.97±0.88, $p=0.001$), euthymia (2.69±1.30, $p=0.001$), and HCs (2.56±0.67, $p=0.002$). Nonetheless, no statistically significant differences were found among the different groups in pmaEDA ($F(3, 67)=1.772$, $p=0.161$). Age, sex, and medical comorbidity did not influence the former results.

[Figure 2 goes here]

Intra-subject longitudinal comparisons between acute mood episodes (T0) and remission (T1) for mania and depression are shown in **Figure 3**. After clinical remission, patients with mania presented a significant reduction in mEDA ($t(14) = -2.328$, $p=0.035$) and pmEDA ($t(14) = -3.415$, $p = 0.004$), but not for pmaEDA ($t(14) = -0.441$, $p=0.666$). In contrast, patients with bipolar depression showed a significant increase in mEDA ($t(8) = 3.293$, $p=0.011$), pmEDA ($t(8) = 7.114$, $p<0.001$), and pmaEDA ($t(8) = 5.866$, $p<0.001$) after remission. Again, age, sex, and medical comorbidity did not influence the previous results.

[Figure 3 goes here]

Discussion

Despite EDA's long history in mental health research, this is among the first studies reporting both significant inter-subject differences between mood states and intra-subject longitudinal differences during the resolution of a mood episode in BD while continuously monitoring EDA with a wearable device. Our results highlight the potential use of EDA parameters as digital biomarkers of affective (manic and depressive) psychopathology as well as potential digital biomarkers of treatment response during manic and depressive episodes in BD.

First, the inter-subject results comparing different mood states (**Figure 2**) demonstrate that both tonic and phasic EDA components are reduced in patients with bipolar depression compared to BD patients with mania, euthymia, and HC. Previous studies have similarly reported lower levels of tonic EDA in BD patients compared with HC when they were exposed to stressful stimuli (Iacono et al., 1983). Likewise, there are several studies that reported hypoactive EDA parameters (tonic and phasic) on both unipolar and bipolar depression, especially in those cases with active suicidal thoughts (Sarchiapone et al., 2018; Thorell et al., 2013; Williams et al., 1985; Wolfersdorf et al., 1996). A more recent study, also using affective elicitation methods, assessed the EDA phasic and tonic parameters of 10 BD patients during different mood states, showing a reduction of EDA tonic and phasic parameters during depressive episodes compared to euthymia (Greco et al., 2014). It was argued that this reduction could be due to a recovery of sympathetic activity, which may be decreased during depressive episodes (Sarchiapone et al., 2018). However, other studies found that autonomic dysregulation in depression could be driven by decreased parasympathetic or vagal activity (Moretta et al., 2023). Indeed, some studies suggest that only a subgroup of patients with depression shows autonomic dysregulation (Hausberg et al., 2007), which could, in turn, benefit from personalized treatment strategies. A complementary approach is that depression is often characterized by alterations in emotional processing (De Prisco et al., 2022). A decrease in EDA parameters could indicate a diminished physiological response to emotional stimuli. It may suggest reduced emotional reactivity or blunted emotional responses commonly observed in individuals with depression (Imbault and Kuperman, 2018). These findings need to be further studied and corroborated in bipolar depression.

Second, our longitudinal results (**Figure 3**) demonstrate that people with bipolar depression showed an increase in EDA tonic and phasic parameters after clinical remission, reaching levels comparable to

euthymic patients and HC, thus normalizing initially reduced EDA parameters. Interestingly, another group also found a normalization of EDA tonic and phasic parameters in patients with bipolar depression after returning to a euthymic state (Greco et al., 2014). These results can be interpreted as the normalization of hypoactive EDA (reduced sympathetic response to stimuli) during depression. In fact, the increase of the amplitude (pmaEDA) after remission is noteworthy (**Figure 3**).

Moreover, patients with manic episodes showed a reduction in phasic and tonic EDA parameters after symptoms improvement. This is the first study that reports such longitudinal changes in manic patients compared to clinical remission. Previous literature (Greco et al., 2014) reported a reduction only in the phasic components in one patient with mixed symptoms after reaching clinical remission. Our results may be interpreted as the ~~normalization~~ reduction of a probably excessive sympathetic activity during manic episodes (Swann et al., 1991).

It is important to highlight that most of the aforementioned studies are limited by their small sample sizes, which complicates the generalizability of the results (Hausberg et al., 2007). Moreover, most of these studies only assessed participants with affective disorders at clinical stability or euthymia. The lack or paucity of affective symptoms during euthymia and the fact that there is a huge inter-individual variability of "normal" or physiological EDA parameters might also hinder previous assumptions. This is added to the fact that only a minority of studies assessed people with BD, and most focused on depression without distinguishing between bipolar and unipolar depression. Of note, the increased prevalence of manic symptoms during bipolar depression (Corponi et al., 2020; Fagiolini and Cuomo, 2023; Pacchiarotti et al., 2020) may derive in differences regarding autonomic dysregulation (Hausberg et al., 2007), which have not yet been studied in-depth. Moreover, the methods used to measure EDA in the studies differed highly and most included devices in laboratory settings and involved elicitation stimuli. While most studies used an elicitation method in an experimental setting, we showed that registering the same parameters in a real-world clinical setting with a user-friendly device is feasible and allows to continuously collect EDA parameters also showing significant differences.

In sum, our results suggest that EDA may be a plausible marker for bipolar depression, but also a state-related marker of treatment response both for depressive and manic episodes in BD. We provide a first indication that differential sympathetic functioning according to mood states in BD can be captured in a real-world setting without the need of elicitation methods. If our results are validated in other studies,

EDA ecological monitoring might provide several opportunities for early detection (and intervention) of depressive symptoms, and might aid at assessing early response to treatments both in mania and bipolar depression.

Additionally, there are many other promising physiological parameters that can be collected with wearables (Van Assche et al., 2022). For instance, Heart Rate Variability (HRV) has also shown an autonomic dysfunction in BD (Faurholt-Jepsen et al., 2017). In the context of this study, we showed preliminary evidence that the combination of physiological raw data (including acceleration, temperature, heart rate, and EDA) using deep learning methods allowed to identify mood episodes and specific symptoms of mania and depression quantitatively (Anmella et al., 2023; Corponi et al., 2023; Li et al., 2022). As with EDA, derived features from other physiological parameters (HRV, acceleration, temperature) could provide new insights into the physiopathology of affective symptoms and personalization of treatments in BD, and possibly other psychiatric disorders (Fusar-Poli et al., 2022; Orsolini et al., 2020; Vieta, 2015). Future steps in our research include exploring frequency-domain features from EDA (Föll et al., 2021) which have been regarded as more consistent and related to sympathetic activity, with specific indexes such as the time-varying EDA index of sympathetic control (TVSymp) (Posada-Quintero et al., 2016).

Limitations

Several limitations in our study should be pointed out beyond its exploratory nature and the limited sample size, which warrants replication in larger samples. First, the novel method of continuously collecting EDA in real-world conditions with a wearable device and without stress elicitation methods. This differs from most previous studies employing diverse elicitation methods particularly to assess tonic EDA parameters (Greco et al., 2014; Sarchiapone et al., 2018). This limits comparability of our results with previous studies. In order to validate these results compared to previous evidence, we will study EDA reactivity conditioned to a stress-elicitation stimulus through a Stroop test. Note that in this study, even that patients' EDA was recorded during similar external conditions (e.g., inpatient unit admission), stressful events were not controlled for and dependent on external conditions. In addition, other factors such as age, sex, pharmacological treatments, comorbidities, and individual variations could also influence EDA measurements (Ilzarbe and Vieta, 2023). Some of these variables (i.e., age, sex, medical comorbidities) were controlled for. It is also important to note that both external (ambient temperature,

humidity) and individual factors (physical activity, skin hydration, stimulants consumption, medications, comorbid and medical conditions such as hyperhidrosis) can affect EDA measurements. In the case of the inpatients, some of the external factors were uniform across the sample as the inpatient unit´s ambient temperature and humidity are centrally controlled, illicit substances and tobacco are strictly forbidden, caffeine consumption is not permitted and only limited physical activity is allowed. Furthermore, analyses were performed without considering sleep versus wake times, in which sympathetic activity (and consequently EDA parameters) have a huge variability and may have influenced the results. Considering the expected marked differences in EDA between wake and sleep times, further analyses of the current work will include the respective sub-analyses of EDA between sleep and wake times using automated sleep detection methods. On the other hand, in comparison to previous studies including few patients usually at euthymia, our research has included a considerable number of patients with BD on acute mood episodes (usually severe requiring inpatient admission; **Table 2**) and conducting longitudinal follow-up registers. Of note, in this population recruitment is highly challenging, but on the other hand guarantees the presence of severe affective symptomatology, which is the main objective of this study. Another strength worth mentioning is the possibility of capturing EDA with a research-wearable device collecting fine-grained and longitudinal data, which was pre-processed, clean from most artifacts and analyzed with an automated open-source package developed for this specific wearable, thus allowing other research groups to replicate our results and possibly expanding analyses to diverse biomedical studies (de Looff et al., 2022).

Conclusion

Patients with bipolar depression showed significantly reduced tonic and phasic EDA parameters compared to the other groups, which were normalized after clinical remission. Manic patients showed a significant reduction of tonic and phasic EDA parameters after clinical remission. EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments both in mania and bipolar depression. Further and more uniform studies are needed to fully establish the reliability and validity of EDA to generalize as a marker of illness activity and treatment response in BD and other psychiatric populations.

Authors' Contributions

GA and DH-M were responsible for study planning, project conception, and coordination. A Mas, MS, CV-P, MV, IP, A Benabarre, IG, AG-P, MG, A Bastidas, and IA were responsible for recruitment. DH-M, A Mas, PdL, FC, BML, MDP, VO, and GF were responsible for data analysis. GA and DH-M were responsible for manuscript preparation. All authors revised the final manuscript.

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Data Availability

The data supporting the findings of this study are available upon request from the corresponding author.

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Conflict of interests

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, Rovi, Casen Recordati, and Angelini, with no financial or other relationship relevant to the subject of this article.

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References

Anmella, G., Corponi, F., Li, B.M., Mas, A., Sanabra, M., Pacchiarotti, I., Valentí, M., Grande, I., Benabarre, A., Giménez-Palomo, A., Garriga, M., Agasi, I., Bastidas, A., Cavero, M., Fernández-Plaza, T., Arbelo, N., Bioque, M., García-Rizo, C., Verdolini, N., Madero, S., Murru, A., Amoretti, S., Martínez-Aran, A., Ruiz, V., Fico, G., De Prisco, M., Oliva, V., Solanes, A., Radua, J., Samalin, L., Young, A.H., Vieta, E., Vergari, A., Hidalgo-Mazzei, D., 2023. Exploring Digital Biomarkers of Illness Activity in Mood Episodes: Hypotheses Generating and Model Development Study. JMIR Mhealth Uhealth 11, e45405. https://doi.org/10.2196/45405

APA, 2013. Diagnostic and statistical manual of mental disorders : DSM-5. American Psychiatric Association, Arlington, VA.

Babrak, L.M., Menetski, J., Rebhan, M., Nisato, G., Zinggeler, M., Brasier, N., Baerenfaller, K., Brenzikofer, T., Baltzer, L., Vogler, C., Gschwind, L., Schneider, C., Streiff, F., Groenen, P.M.A., Miho, E., 2019. Traditional and Digital Biomarkers: Two Worlds Apart? Digit Biomark 3, 92–102. https://doi.org/10.1159/000502000

Boucsein, W., Fowles, D.C., Grimnes, S., Ben-Shakhar, G., Roth, W.T., Dawson, M.E., Filion, D.L., 2012. Publication recommendations for electrodermal measurements. Psychophysiology 49, 1017–1034. https://doi.org/10.1111/J.1469-8986.2012.01384.X

Carvalho, A.F., Solmi, M., Sanches, M., Machado, M.O., Stubbs, B., Ajnakina, O., Sherman, C., Sun, Y.R., Liu, C.S., Brunoni, A.R., Pigato, G., Fernandes, B.S., Bortolato, B., Husain, M.I., Dragioti, E., Firth, J., Cosco, T.D., Maes, M., Berk, M., Lanctôt, K.L., Vieta, E., Pizzagalli, D.A., Smith, L., Fusar-Poli, P., Kurdyak, P.A., Fornaro, M., Rehm, J., Herrmann, N., 2020. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. Translational Psychiatry 2020 10:1 10, 1–13. https://doi.org/10.1038/s41398-020-0835-5

Chen, C.-H., Suckling, J., Lennox, B.R., Ooi, C., Bullmore, E.T., 2011. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord 13, 1–15. https://doi.org/10.1111/j.1399-5618.2011.00893.x

Colom, F., Vieta, E., Martínez-Arán, A., Garcia-Garcia, M., Reinares, M., Torrent, C., Goikolea, J.M., Banús, S., Salamero, M., 2002. [Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale]. Med Clin (Barc) 119, 366–71.

Corponi, F., Anmella, G., Verdolini, N., Pacchiarotti, I., Samalin, L., Popovic, D., Azorin, J.M., Angst, J., Bowden, C.L., Mosolov, S., Young, A.H., Perugi, G., Vieta, E., Murru, A., 2020. Symptom networks in acute depression across bipolar and major depressive disorders: A network analysis on a large, international, observational study. Eur Neuropsychopharmacol 35, 49–60. https://doi.org/10.1016/J.EURONEURO.2020.03.017

Corponi, F., Li, B.M., Anmella, G., Mas, A., Sanabra, M., Vieta, E., Group, I., Lawrie, S.M., Whalley, H.C., Hidalgo-Mazzei, D., Vergari, A., 2023. Automated mood disorder symptoms monitoring from multivariate time-series sensory data: Getting the full picture beyond a single number. medRxiv 2023.03.25.23287744. https://doi.org/10.1101/2023.03.25.23287744

Critchley, H.D., 2002. Review: Electrodermal Responses: What Happens in the Brain. The Neuroscientist 8, 132–142. https://doi.org/10.1177/107385840200800209

de Looff, P., Duursma, R., Noordzij, M., Taylor, S., Jaques, N., Scheepers, F., de Schepper, K., Koldijk, S., 2022. Wearables: An R Package With Accompanying Shiny Application for Signal Analysis of a Wearable Device Targeted at Clinicians and Researchers. Front Behav Neurosci 16. https://doi.org/10.3389/FNBEH.2022.856544

De Prisco, M., Oliva, V., Fico, G., Fornaro, M., de Bartolomeis, A., Serretti, A., Vieta, E., Murru, A., 2022. Defining clinical characteristics of emotion dysregulation in bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 142, 104914. https://doi.org/10.1016/J.NEUBIOREV.2022.104914

Empatica, 2022. Empatica E4 [WWW Document]. URL https://www.empatica.com/en-gb/research/e4/ (accessed 5.23.22).

Fagiolini, A., Cuomo, A., 2023. Treating major depressive disorder with mixed features. Eur Neuropsychopharmacol 69, 58–59. https://doi.org/10.1016/J.EURONEURO.2023.01.004

Faurholt-Jepsen, M., Kessing, L.V., Munkholm, K., 2017. Heart rate variability in bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 73, 68–80. https://doi.org/10.1016/j.neubiorev.2016.12.007

Föll, S., Maritsch, M., Spinola, F., Mishra, V., Barata, F., Kowatsch, T., Fleisch, E., Wortmann, F., 2021. FLIRT: A feature generation toolkit for wearable data. Comput Methods Programs Biomed 212, 106461. https://doi.org/10.1016/J.CMPB.2021.106461

Fusar-Poli, P., Manchia, M., Koutsouleris, N., Leslie, D., Woopen, C., Calkins, M.E., Dunn, M., Tourneau, C. Le, Mannikko, M., Mollema, T., Oliver, D., Rietschel, M., Reininghaus, E.Z., Squassina, A., Valmaggia, L., Kessing, L.V., Vieta, E., Correll, C.U., Arango, C., Andreassen, O.A., 2022. Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. Eur Neuropsychopharmacol 63, 17–34. https://doi.org/10.1016/J.EURONEURO.2022.08.001

Greco, A., Valenza, G., Lanata, A., Rota, G., Scilingo, E.P., 2014. Electrodermal activity in bipolar patients during affective elicitation. IEEE J Biomed Health Inform 18, 1865–1873. https://doi.org/10.1109/JBHI.2014.2300940

Hamilton, M., 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23, 56–62.

Hausberg, M., Hillebrand, U., Kisters, K., 2007. Addressing sympathetic overactivity in major depressive disorder. J Hypertens 25, 2004–2005. https://doi.org/10.1097/HJH.0B013E3282EF9819

Hsin, H., Fromer, M., Peterson, B., Walter, C., Fleck, M., Campbell, A., Varghese, P., Califf, R., 2018. Transforming Psychiatry into Data-Driven Medicine with Digital Measurement Tools. NPJ Digit Med 1, 37. https://doi.org/10.1038/s41746-018-0046-0

Iacono, W.G., Lykken, D.T., Peloquin, L.J., Lumry, A.E., Valentine, R.H., Tuason, V.B., 1983. Electrodermal Activity in Euthymic Unipolar and Bipolar Affective Disorders: A Possible Marker for Depression. Arch Gen Psychiatry 40, 557–565. https://doi.org/10.1001/archpsyc.1983.01790050083010

Ilzarbe, L., Vieta, E., 2023. The elephant in the room: Medication as confounder. European Neuropsychopharmacology 71, 6–8. https://doi.org/10.1016/J.EURONEURO.2023.03.001

Imbault, C., Kuperman, V., 2018. Emotional reactivity and perspective-taking in individuals with and without severe depressive symptoms. Scientific Reports 2018 8:1 8, 1–8. https://doi.org/10.1038/s41598-018-25708-x

Johnson, K.T., Picard, R.W., 2020. Advancing Neuroscience through Wearable Devices. Neuron 108, 8–12. https://doi.org/10.1016/j.neuron.2020.09.030

Li, B.M., Corponi, F., Anmella, G., Mas, A., Sanabra, M., Hidalgo-Mazzei, D., Vergari, A., 2022. Inferring mood disorder symptoms from multivariate time-series sensory data.

Miller, C.J., Johnson, S.L., Eisner, L., 2009. Assessment Tools for Adult Bipolar Disorder. Clin Psychol (New York) 16, 188. https://doi.org/10.1111/J.1468-2850.2009.01158.X

Moretta, T., Kaess, M., Koenig, J., 2023. A comparative evaluation of resting state proxies of sympathetic and parasympathetic nervous system activity in adolescent major depression. J Neural Transm (Vienna) 130, 135–144. https://doi.org/10.1007/S00702-022-02577-3

Orsolini, L., Fiorani, M., Volpe, U., 2020. Digital Phenotyping in Bipolar Disorder: Which Integration with Clinical Endophenotypes and Biomarkers? Int J Mol Sci 21, 1–21. https://doi.org/10.3390/IJMS21207684

Pacchiarotti, I., Anmella, G., Colomer, L., Vieta, E., 2020. How to treat mania. Acta Psychiatr Scand 142, 173–192. https://doi.org/10.1111/acps.13209

Posada-Quintero, H.F., Chon, K.H., 2020. Innovations in Electrodermal Activity Data Collection and Signal Processing: A Systematic Review. Sensors (Basel) 20. https://doi.org/10.3390/S20020479

Posada-Quintero, H.F., Florian, J.P., Orjuela-Cañón, Á.D., Chon, K.H., 2016. Highly sensitive index of sympathetic activity based on time-frequency spectral analysis of electrodermal activity. Am J Physiol Regul Integr Comp Physiol 311, R582–R591. https://doi.org/10.1152/AJPREGU.00180.2016

Ramos-Brieva, J.A., Cordero-Villafafila, A., 1988. A new validation of the Hamilton Rating Scale for Depression. J Psychiatr Res 22, 21–8.

Sarchiapone, M., Gramaglia, C., Iosue, M., Carli, V., Mandelli, L., Serretti, A., Marangon, D., Zeppegno, P., 2018. The association between electrodermal activity (EDA), depression and suicidal behaviour: A systematic review and narrative synthesis. BMC Psychiatry 18. https://doi.org/10.1186/s12888-017-1551-4

Setz, C., Arnrich, B., Schumm, J., La Marca, R., Tröster, G., Ehlert, U., 2010. Discriminating stress from cognitive load using a wearable EDA device. IEEE Trans Inf Technol Biomed 14, 410–417. https://doi.org/10.1109/TITB.2009.2036164

Swann, A.C., Secunda, S.K., Koslow, S.H., Katz, M.M., Bowden, C.L., Maas, J.W., Davis, J.M., Robins, E., 1991. Mania: Sympathoadrenal function and clinical state. Psychiatry Res 37, 195–205. https://doi.org/10.1016/0165-1781(91)90075-Z

Taylor, S., Jaques, N., Chen, W., Fedor, S., Sano, A., Picard, R., 2015. Automatic identification of artifacts in electrodermal activity data. Annu Int Conf IEEE Eng Med Biol Soc 2015, 1934–1937. https://doi.org/10.1109/EMBC.2015.7318762

Thorell, L.H., Wolfersdorf, M., Straub, R., Steyer, J., Hodgkinson, S., Kaschka, W.P., Jandl, M., 2013. Electrodermal hyporeactivity as a trait marker for suicidal propensity in uni- and bipolar depression. J Psychiatr Res 47, 1925–1931. https://doi.org/10.1016/J.JPSYCHIRES.2013.08.017

Tohen, M., Frank, E., Bowden, C.L., Colom, F., Ghaemi, S.N., Yatham, L.N., Malhi, G.S., Calabrese, J.R., Nolen, W.A., Vieta, E., Kapczinski, F., Goodwin, G.M., Suppes, T., Sachs, G.S., Chengappa, K.R., Grunze, H., Mitchell, P.B., Kanba, S., Berk, M., 2009. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 11, 453–473. https://doi.org/10.1111/j.1399-5618.2009.00726.x

Van Assche, E., Antoni Ramos-Quiroga, J., Pariante, C.M., Sforzini, L., Young, A.H., Flossbach, Y., Gold, S.M., Hoogendijk, W.J.G., Baune, B.T., Maron, E., 2022. Digital tools for the assessment of pharmacological treatment for depressive disorder: State of the art. Eur Neuropsychopharmacol 60, 100–116. https://doi.org/10.1016/J.EURONEURO.2022.05.007

van Lier, H.G., Pieterse, M.E., Garde, A., Postel, M.G., de Haan, H.A., Vollenbroek-Hutten, M.M.R., Schraagen, J.M., Noordzij, M.L., 2020. A standardized validity assessment protocol for physiological signals from wearable technology: Methodological underpinnings and an application to the E4 biosensor. Behav Res Methods 52, 607–629. https://doi.org/10.3758/S13428-019-01263-9/TABLES/7

Vasudevan, S., Saha, A., Tarver, M.E., Patel, B., 2022. Digital biomarkers: Convergence of digital health technologies and biomarkers. npj Digital Medicine 2022 5:1 5, 1–3. https://doi.org/10.1038/s41746-022-00583-z

Vieta, E., 2015. La medicina personalizada aplicada a la salud mental: la psiquiatría de precisión. Rev Psiquiatr Salud Ment 8, 117–118. https://doi.org/10.1016/j.rpsm.2015.03.003

Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., Gao, K., Miskowiak, K.W., Grande, I., 2018. Bipolar disorders. Nature Reviews Disease Primers 2018 4:1 4, 1–16. https://doi.org/10.1038/nrdp.2018.8

Williams, K.M., Iacono, W.G., Remick, R.A., 1985. Electrodermal activity among subtypes of depression. Biol Psychiatry 20, 158–162. https://doi.org/10.1016/0006-3223(85)90075-7

Wolfersdorf, M., Straub, R., Barg, Th., Keller, F., 1996. Depression und EDA-Kennwerte in einem Habituationsexperiment. Fortschritte der Neurologie · Psychiatrie 64, 105–109. https://doi.org/10.1055/s-2007-996376

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133, 429–35.

Electrodermal activity in bipolar disorder: differences between mood episodes and clinical remission using a wearable device in a real-world clinical setting.

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Abstract

Background: Bipolar disorder (BD) lacks objective measures for illness activity and treatment response. Electrodermal activity (EDA) is a quantitative measure of autonomic function, which is altered in manic and depressive episodes. We aimed to explore differences in EDA (1) inter-individually: between patients with BD on acute mood episodes, euthymic states and healthy controls (HC), and (2) intra-individually: longitudinally within patients during acute mood episodes of BD and after clinical remission.

Methods: A longitudinal observational study. EDA was recorded using a research-grade wearable in patients with BD during acute manic and depressive episodes and at clinical remission. Euthymic BD patients and HC were recorded during a single session. We compared EDA parameters derived from the tonic (mean EDA, mEDA) and phasic components (EDA peaks per minute, pmEDA, and EDA peaks mean amplitude, pmaEDA). Inter- and intra-individual comparisons were computed respectively with ANOVA and paired T-tests.

Results: 49 patients with BD (15 manic, 9 depressed, and 25 euthymic), and 19 HC were included. Patients with bipolar depression showed significantly reduced mEDA ($p=0.003$) and pmEDA ($p=0.001$), which increased to levels similar to euthymia or HC after clinical remission (mEDA, $p=0.011$; pmEDA, $p<0.001$; pmaEDA, $p<0.001$). Manic patients showed no differences compared to euthymic patients and HCs, but a significant reduction of tonic and phasic EDA parameters after clinical remission (mEDA, $p=0.035$; pmEDA, $p=0.004$).

Limitations: Limited sample size, high inter-individual variability of EDA parameters, limited comparability to previous studies and non-adjustment for medication.

Conclusion: EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments in mania and bipolar depression.

Keywords: Electrodermal activity, bipolar disorder, depression, mania, biomarker, treatment response.

Word count: 3,460 words

Highlights

- EDA is reduced during bipolar depression and increases after remission.
- Ecological monitoring of EDA might allow early detection of depressive symptoms.
- Electrodermal activity (EDA) is reduced after remission of a manic episode.
- EDA might aid to asses early response to treatment in mania and bipolar depression.

Introduction

Bipolar disorder (BD) is a chronic mental health condition characterized by pathological mood states encompassing depressive and manic episodes. Beyond mood episodes and despite optimal treatment, BD can still have enduring detrimental long-term consequences on individual's functionality, quality of life, cognition, and morbimortality (Vieta et al., 2018).

Assessments for diagnosis, illnesss activity (e.g. mood episodes, symptom severity), and treatment response in BD are still based on subjective reports from clinical interviews, questionnaires, and standardized scales (Miller et al., 2009). Despite the intensive research in the field to find specific and objective biomarkers, none of the few promising biomarkers identified has been implemented in real-world clinical practice so far (Carvalho et al., 2020).

Recent advances in wearable technologies has allowed to ubiquitously collect in real-world, ecological settings a multitude of physiological signals, including heart rate, temperature, blood pressure, and also electrodermal activity (EDA), which was previously restricted to laboratory or hospital settings (Hsin et al., 2018). Compared to traditional methods for measuring the previous physiological data, digital devices allow for continuous, longitudinal, granular, unobtrusive, and usually cost-efficient measurements (Babrak et al., 2019). Over the last decade, there has been increasing interest in exploring the association of physiological digital data with behavioural alterations in psychiatric disorders. The associations between these digital data and disease-related outcomes have been denominated digital biomarkers (Vasudevan et al., 2022).

One physiological signal that has been studied for more than a century is EDA, also known as galvanic skin response. EDA has been investigated as a potential biomarker in mood disorders in numerous laboratory studies and is seen as a cost-effective method to assess the arousal of the sympathetic nervous autonomous system, and has been a popular index to study the significance and intensity of various laboratory induced (emotional) stimuli (Boucsein et al., 2012; Johnson and Picard, 2020; Sarchiapone et al., 2018; van Lier et al., 2020). The EDA signal is an electrical manifestation of the sympathetic innervation of the sweat glands. Emotion-evoked increased sweating augments the electrical conductance of the skin. Therefore, EDA is believed to represent a quantitative measure of autonomic function and an objective assessment of cognitive arousal (Setz et al., 2010). EDA makes it theoretically possible to estimate the

time and amplitude of stimuli generated from control centres in the brain by interpreting the manifestation of their arrival at the skin level, which is observable in the EDA signal. In sum, EDA is a the result of different processes in the skin and seems to be solely innervated by the sympathetic nervous system (Posada-Quintero and Chon, 2020).

EDA can be decomposed into tonic and phasic components: tonic activity varies relatively slowly and is also referred to as skin conductance level (SCL), while phasic activity varies rapidly in response to stimuli such as stress and is also referred to as the skin conductance response (SCR). SCR is characterized by a rapid incline to a peak and then a slower decline back to the individual's SCL (**Figure 1**) (Boucsein et al., 2012). Both are strongly and dynamically linked to the sympathetic nervous autonomous system via sweating regulation controlled by brain regions implicated in emotion, attention, and cognition such as the prefrontal cortex, amygdala, hippocampus, and cingulate cortex (Critchley, 2002).

[Figure 1 goes here]

Coincidentally, meta-analyses of functional magnetic resonance imaging (fMRI) studies have revealed dysfunction of these same areas in patients with BD (Chen et al., 2011). In addition, several studies showed EDA hypo-reactivity in depression and suicidal behaviour (Sarchiapone et al., 2018). To date, only a few studies have explored EDA's potential in differentiating mood episodes or assessing clinical response in BD (Greco et al., 2014). Furthermore, to our knowledge, no studies have been yet performed using a wearable device in an ecological setting on BD patients. Considering the recent possibility of continuously monitoring EDA with unobtrusive wearables, we aimed to explore differences in EDA (1) inter-individually: between patients with BD on acute mood episodes or euthymic states and healthy controls (HC), and (2) intra-individually: longitudinally within patients during an acute mood episode of BD and after clinical remission in a real-world clinical setting.

Methods

This is a longitudinal observational study including patients with BD on acute manic and depressive episodes or euthymic phases, according to DSM-5 criteria (APA, 2013). Patients were recruited from various clinical settings including inpatient, home-treatment and outpatient units from the Bipolar and Depressive Disorders Unit at the Hospital Clínic de Barcelona. Further details on inclusion/exclusion criteria have been reported elsewhere (Anmella et al., 2023). Participants needed to provide written informed consent. In patients on acute episodes, their capacity to provide informed consent was assessed at inclusion and re-assessed after remission.

Sociodemographic and clinical variables (i.e., current and previous diagnosis, duration of illness, psychiatric and medical comorbidities) were collected. Manic and depressive symptoms were assessed respectively using standardized psychometric scales: the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978) and the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafafila, 1988). HC were recruited from a convenience sample of researchers and relatives.

EDA was recorded using a research-grade wearable (Empatica E4 (Empatica, 2022)) in patients with BD during acute manic and depressive episodes and at clinical remission, defined as standardized clinical scores ≤7 at YMRS and HDRS (i.e., symptoms absent or nearly absent) (Tohen et al., 2009). Euthymic BD patients and HC were recorded during a single session. All sessions lasted approximately 48 hours, due to limited battery life of the device.

We compared continuous registers of EDA parameters from the tonic (i.e., mean EDA, as proxy for the SCL) and phasic components (i.e., EDA peaks per minute, EDA peaks mean amplitude, extracted from the SCR) in patients with BD (1) inter-individually during acute manic and depressive episodes, euthymia, and healthy controls (HC), and (2) intra-individually during acute manic and depressive episodes, and after remission of the episode.

Data collected by the wearables were processed with the “Wearables” which is an R package designed to pre-process, detect artifacts, and extract features in data from the Empatica E4 (de Looff et al., 2022). Artifact detection in EDA signal is performed after pre-processing following the algorithm developed by

Taylor et al. (Taylor et al., 2015). In short, several features are extracted from the EDA signal, which is put into an algorithm that classifies for each segment of 5 seconds, whether this segment contains an artifact. The algorithm is a support vector machine pre-trained on expert data. Calculations are performed on the segment and one-second and half-a-second wavelet decompositions of the measurements. The pre-training also determined which of the features are used in the support vector machine algorithm. The algorithm has two settings, binary classification (artifact and no artifact) and ternary classification (artifact, unclear, and no artifact). The "Wearables" package can be used in combination with a user interface called the E4 dashboard. Researchers can visualize the physiological signals and have several algorithms available to detect artifacts in the raw physiological signals, and extract relevant features for analysis. A *batch* analysis function is available to extract relevant features for all the physiological signals that are available from the Empatica E4 (acceleration, blood volume pulse, heart rate, interbeat-interval, EDA, and temperature). For the current study, the resulting relevant EDA features were extracted for each subject´s session, specifically mean EDA (mEDA), EDA peaks per minute (pmEDA) and EDA peaks mean amplitude (pmaEDA). Statistical analyses were computed with SPSS 28 (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Normality of EDA parameters were assessed using the Shapiro-Wilk test. Accordingly, inter- and intra-individual comparisons were computed respectively with ANOVA with Tukey's post-hoc test for multiple comparisons, and paired T-tests. Subsequently, significant results were controlled for covariates that could affect dependent variables such as age, sex and medical comorbidity with an ANCOVA and ANCOVA for repeated measures.

Results

A total of 49 subjects with the diagnosis of BD (15 manic, 9 depressed, and 25 euthymic) and 19 HCs were recruited and included in the analyses. Sociodemographic and clinical information of both groups is reported in **Table 1**, and is detailed according to each mood episode group in **Table 2**. Clinical information of patients with BD, including the type of BD, substance use disorder (SUD), illness duration, presence of psychotic features during an episode, and affective symptoms' scores during acute mood episodes and after remission are detailed in **Table 2**.

[Table 1 goes here]

[Table 2 goes here]

The BD and HC population were comparable in terms of age, sex, and medical comorbidities (**Table 1**). There were also no significant differences between mood episode groups (**Table 2**). Most patients had BD type 1 and more than 75% did not have history of SUD. Only manic patients presented with psychotic symptoms during acute episodes (60%). Duration of illness was shorter ($F=3.23$, $p=0.049$) for patients with mania (6.6±7.7 years) compared to patients with depression (17.1±11.3 years) and euthymia(13.8±8.9 years). Mean YMRS for patients with manic episodes was 26.8±4.7 at T0, with a reduction to 3.7±4.3 at T1. Mean HDRS for patients with bipolar depression was 18.4±4.7 at T0, with a reduction to 3.9±2.1 at T1 (**Table 2**). A total of 3,227 hours (approximately 134 days) were recorded at T0 for the whole sample averaging 47.5±6.9 hours per session (SD=7.1), while 1,124 hours (approximately 47 days) were recorded at T1 follow-ups of BD patients with an average of 46.8±7.7 hours per session. For T0, the median percentage of data per recording session dropped from further analysis due to artifact detection was 31.89; interquartile range (IQR) 28.05 for mania, 10.72; IQR 72.46 for depression, 13.23; IQR 17.83 for euthymia, and 14.50; IQR 14.09 for HC. There were no significant differences on discarded segments due to artifact detection between groups ($H(3) = 7.06$, $p = 0.07$). For T1, the median percentage of data per recording session dropped from further analysis due to artifact detection was 12.40; IQR 17.53 for mania, and 17.36; IQR 57.60 for depression. There were no significant differences on discarded segments due to artifact detection between groups ($U = 47.0$, $p = 0.22$). The explored EDA variables (mEDA, pmEDA, pmaEDA) followed a normal distribution according to the Shapiro-Wilk test ($p > 0.20$).

Inter-subject comparisons of EDA parameters are shown in **Figure 2**. Patients with bipolar depression (0.43±0.22) had a statistically significantly lower mEDA ($F(3, 67) = 5.860$, $p=0.003$) when compared to mania (2.05±1.16, $p=0.003$), euthymia (1.92±1.38, $p=0.004$), and HCs (1.76±0.62, $p=0.016$). Similarly, pmEDA were significantly lower ($F(3, 67) = 8.062$, $p=0.001$) in patients with bipolar depression (1.01±0.72) when compared to mania (2.97±0.88, $p=0.001$), euthymia (2.69±1.30, $p=0.001$), and HCs (2.56±0.67, $p=0.002$). Nonetheless, no statistically significant differences were found among the different groups in pmaEDA ($F(3, 67)=1.772$, $p=0.161$). Age, sex, and medical comorbidity did not influence the former results.

[Figure 2 goes here]

Intra-subject longitudinal comparisons between acute mood episodes (T0) and remission (T1) for mania and depression are shown in **Figure 3**. After clinical remission, patients with mania presented a significant reduction in mEDA ($t(14) = -2.328$, $p=0.035$) and pmEDA ($t(14) = -3.415$, $p = 0.004$), but not for pmaEDA ($t(14) = -0.441$, $p=0.666$). In contrast, patients with bipolar depression showed a significant increase in mEDA ($t(8) = 3.293$, $p=0.011$), pmEDA ($t(8) = 7.114$, $p<0.001$), and pmaEDA ($t(8) = 5.866$, $p<0.001$) after remission. Again, age, sex, and medical comorbidity did not influence the previous results.

[Figure 3 goes here]

Discussion

Despite EDA's long history in mental health research, this is among the first studies reporting both significant inter-subject differences between mood states and intra-subject longitudinal differences during the resolution of a mood episode in BD while continuously monitoring EDA with a wearable device. Our results highlight the potential use of EDA parameters as digital biomarkers of affective (manic and depressive) psychopathology as well as potential digital biomarkers of treatment response during manic and depressive episodes in BD.

First, the inter-subject results comparing different mood states (**Figure 2**) demonstrate that both tonic and phasic EDA components are reduced in patients with bipolar depression compared to BD patients with mania, euthymia, and HC. Previous studies have similarly reported lower levels of tonic EDA in BD patients compared with HC when they were exposed to stressful stimuli (Iacono et al., 1983). Likewise, there are several studies that reported hypoactive EDA parameters (tonic and phasic) on both unipolar and bipolar depression, especially in those cases with active suicidal thoughts (Sarchiapone et al., 2018; Thorell et al., 2013; Williams et al., 1985; Wolfersdorf et al., 1996). A more recent study, also using affective elicitation methods, assessed the EDA phasic and tonic parameters of 10 BD patients during different mood states, showing a reduction of EDA tonic and phasic parameters during depressive episodes compared to euthymia (Greco et al., 2014). It was argued that this reduction could be due to a recovery of sympathetic activity, which may be decreased during depressive episodes (Sarchiapone et al., 2018). However, other studies found that autonomic dysregulation in depression could be driven by decreased parasympathetic or vagal activity (Moretta et al., 2023). Indeed, some studies suggest that only a subgroup of patients with depression shows autonomic dysregulation (Hausberg et al., 2007), which could, in turn, benefit from personalized treatment strategies. A complementary approach is that depression is often characterized by alterations in emotional processing (De Prisco et al., 2022). A decrease in EDA parameters could indicate a diminished physiological response to emotional stimuli. It may suggest reduced emotional reactivity or blunted emotional responses commonly observed in individuals with depression (Imbault and Kuperman, 2018). These findings need to be further studied and corroborated in bipolar depression.

Second, our longitudinal results (**Figure 3**) demonstrate that people with bipolar depression showed an increase in EDA tonic and phasic parameters after clinical remission, reaching levels comparable to

euthymic patients and HC, thus normalizing initially reduced EDA parameters. Interestingly, another group also found a normalization of EDA tonic and phasic parameters in patients with bipolar depression after returning to a euthymic state (Greco et al., 2014). These results can be interpreted as the normalization of hypoactive EDA (reduced sympathetic response to stimuli) during depression. In fact, the increase of the amplitude (pmaEDA) after remission is noteworthy (**Figure 3**).

Moreover, patients with manic episodes showed a reduction in phasic and tonic EDA parameters after symptoms improvement. This is the first study that reports such longitudinal changes in manic patients compared to clinical remission. Previous literature (Greco et al., 2014) reported a reduction only in the phasic components in one patient with mixed symptoms after reaching clinical remission. Our results may be interpreted as the reduction of a probably excessive sympathetic activity during manic episodes (Swann et al., 1991).

It is important to highlight that most of the aforementioned studies are limited by their small sample sizes, which complicates the generalizability of the results (Hausberg et al., 2007). Moreover, most of these studies only assessed participants with affective disorders at clinical stability or euthymia. The lack or paucity of affective symptoms during euthymia and the fact that there is a huge inter-individual variability of "normal" or physiological EDA parameters might also hinder previous assumptions. This is added to the fact that only a minority of studies assessed people with BD, and most focused on depression without distinguishing between bipolar and unipolar depression. Of note, the increased prevalence of manic symptoms during bipolar depression (Corponi et al., 2020; Fagiolini and Cuomo, 2023; Pacchiarotti et al., 2020) may derive in differences regarding autonomic dysregulation (Hausberg et al., 2007), which have not yet been studied in-depth. Moreover, the methods used to measure EDA in the studies differed highly and most included devices in laboratory settings and involved elicitation stimuli. While most studies used an elicitation method in an experimental setting, we showed that registering the same parameters in a real-world clinical setting with a user-friendly device is feasible and allows to continuously collect EDA parameters also showing significant differences.

In sum, our results suggest that EDA may be a plausible marker for bipolar depression, but also a state-related marker of treatment response both for depressive and manic episodes in BD. We provide a first indication that differential sympathetic functioning according to mood states in BD can be captured in a real-world setting without the need of elicitation methods. If our results are validated in other studies,

EDA ecological monitoring might provide several opportunities for early detection (and intervention) of depressive symptoms, and might aid at assessing early response to treatments both in mania and bipolar depression.

Additionally, there are many other promising physiological parameters that can be collected with wearables (Van Assche et al., 2022). For instance, Heart Rate Variability (HRV) has also shown an autonomic dysfunction in BD (Faurholt-Jepsen et al., 2017). In the context of this study, we showed preliminary evidence that the combination of physiological raw data (including acceleration, temperature, heart rate, and EDA) using deep learning methods allowed to identify mood episodes and specific symptoms of mania and depression quantitatively (Anmella et al., 2023; Corponi et al., 2023; Li et al., 2022). As with EDA, derived features from other physiological parameters (HRV, acceleration, temperature) could provide new insights into the physiopathology of affective symptoms and personalization of treatments in BD, and possibly other psychiatric disorders (Fusar-Poli et al., 2022; Orsolini et al., 2020; Vieta, 2015). Future steps in our research include exploring frequency-domain features from EDA (Föll et al., 2021) which have been regarded as more consistent and related to sympathetic activity, with specific indexes such as the time-varying EDA index of sympathetic control (TVSymp) (Posada-Quintero et al., 2016).

Limitations

Several limitations in our study should be pointed out beyond its exploratory nature and the limited sample size, which warrants replication in larger samples. First, the novel method of continuously collecting EDA in real-world conditions with a wearable device and without stress elicitation methods. This differs from most previous studies employing diverse elicitation methods particularly to assess tonic EDA parameters (Greco et al., 2014; Sarchiapone et al., 2018). This limits comparability of our results with previous studies. In order to validate these results compared to previous evidence, we will study EDA reactivity conditioned to a stress-elicitation stimulus through a Stroop test. Note that in this study, even that patients' EDA was recorded during similar external conditions (e.g., inpatient unit admission), stressful events were not controlled for and dependent on external conditions. In addition, other factors such as age, sex, pharmacological treatments, comorbidities, and individual variations could also influence EDA measurements (Ilzarbe and Vieta, 2023). Some of these variables (i.e., age, sex, medical comorbidities) were controlled for. It is also important to note that both external (ambient temperature,

humidity) and individual factors (physical activity, skin hydration, stimulants consumption, medications, comorbid and medical conditions such as hyperhidrosis) can affect EDA measurements. In the case of the inpatients, some of the external factors were uniform across the sample as the inpatient unit´s ambient temperature and humidity are centrally controlled, illicit substances and tobacco are strictly forbidden, caffeine consumption is not permitted and only limited physical activity is allowed. Furthermore, analyses were performed without considering sleep versus wake times, in which sympathetic activity (and consequently EDA parameters) have a huge variability and may have influenced the results. Considering the expected marked differences in EDA between wake and sleep times, further analyses of the current work will include the respective sub-analyses of EDA between sleep and wake times using automated sleep detection methods. On the other hand, in comparison to previous studies including few patients usually at euthymia, our research has included a considerable number of patients with BD on acute mood episodes (usually severe requiring inpatient admission; **Table 2**) and conducting longitudinal follow-up registers. Of note, in this population recruitment is highly challenging, but on the other hand guarantees the presence of severe affective symptomatology, which is the main objective of this study. Another strength worth mentioning is the possibility of capturing EDA with a research-wearable device collecting fine-grained and longitudinal data, which was pre-processed, clean from most artifacts and analyzed with an automated open-source package developed for this specific wearable, thus allowing other research groups to replicate our results and possibly expanding analyses to diverse biomedical studies (de Looff et al., 2022).

Conclusion

Patients with bipolar depression showed significantly reduced tonic and phasic EDA parameters compared to the other groups, which were normalized after clinical remission. Manic patients showed a significant reduction of tonic and phasic EDA parameters after clinical remission. EDA ecological monitoring might provide several opportunities for early detection of depressive symptoms, and might aid at assessing early response to treatments both in mania and bipolar depression. Further and more uniform studies are needed to fully establish the reliability and validity of EDA to generalize as a marker of illness activity and treatment response in BD and other psychiatric populations.

Authors' Contributions

GA and DH-M were responsible for study planning, project conception, and coordination. A Mas, MS, CV-P, MV, IP, A Benabarre, IG, AG-P, MG, A Bastidas, and IA were responsible for recruitment. DH-M, A Mas, PdL, FC, BML, MDP, VO, and GF were responsible for data analysis. GA and DH-M were responsible for manuscript preparation. All authors revised the final manuscript.

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Data Availability

The data supporting the findings of this study are available upon request from the corresponding author.

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Conflict of interests

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, Rovi, Casen Recordati, and Angelini, with no financial or other relationship relevant to the subject of this article.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag, and Lundbeck. IG has received grants and served as consultant, advisor or CME speaker for the following identities: Angelini, Casen Recordati, Ferrer, Janssen Cilag, and Lundbeck, Lundbeck-Otsuka, Luye, SEI Healthcare.

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AHY has received honoraria for lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders.

EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work;

DHM has received CME-related honoraria and served as consultant for Abbott, Angelini, Ethypharm Digital Therapy and Janssen-Cilag.

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References

Anmella, G., Corponi, F., Li, B.M., Mas, A., Sanabra, M., Pacchiarotti, I., Valentí, M., Grande, I., Benabarre, A., Giménez-Palomo, A., Garriga, M., Agasi, I., Bastidas, A., Cavero, M., Fernández-Plaza, T., Arbelo, N., Bioque, M., García-Rizo, C., Verdolini, N., Madero, S., Murru, A., Amoretti, S., Martínez-Aran, A., Ruiz, V., Fico, G., De Prisco, M., Oliva, V., Solanes, A., Radua, J., Samalin, L., Young, A.H., Vieta, E., Vergari, A., Hidalgo-Mazzei, D., 2023. Exploring Digital Biomarkers of Illness Activity in Mood Episodes: Hypotheses Generating and Model Development Study. JMIR Mhealth Uhealth 11, e45405. https://doi.org/10.2196/45405

APA, 2013. Diagnostic and statistical manual of mental disorders : DSM-5. American Psychiatric Association, Arlington, VA.

Babrak, L.M., Menetski, J., Rebhan, M., Nisato, G., Zinggeler, M., Brasier, N., Baerenfaller, K., Brenzikofer, T., Baltzer, L., Vogler, C., Gschwind, L., Schneider, C., Streiff, F., Groenen, P.M.A., Miho, E., 2019. Traditional and Digital Biomarkers: Two Worlds Apart? Digit Biomark 3, 92–102. https://doi.org/10.1159/000502000

Boucsein, W., Fowles, D.C., Grimnes, S., Ben-Shakhar, G., Roth, W.T., Dawson, M.E., Filion, D.L., 2012. Publication recommendations for electrodermal measurements. Psychophysiology 49, 1017–1034. https://doi.org/10.1111/J.1469-8986.2012.01384.X

Carvalho, A.F., Solmi, M., Sanches, M., Machado, M.O., Stubbs, B., Ajnakina, O., Sherman, C., Sun, Y.R., Liu, C.S., Brunoni, A.R., Pigato, G., Fernandes, B.S., Bortolato, B., Husain, M.I., Dragioti, E., Firth, J., Cosco, T.D., Maes, M., Berk, M., Lanctôt, K.L., Vieta, E., Pizzagalli, D.A., Smith, L., Fusar-Poli, P., Kurdyak, P.A., Fornaro, M., Rehm, J., Herrmann, N., 2020. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. Translational Psychiatry 2020 10:1 10, 1–13. https://doi.org/10.1038/s41398-020-0835-5

Chen, C.-H., Suckling, J., Lennox, B.R., Ooi, C., Bullmore, E.T., 2011. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord 13, 1–15. https://doi.org/10.1111/j.1399-5618.2011.00893.x

Colom, F., Vieta, E., Martínez-Arán, A., Garcia-Garcia, M., Reinares, M., Torrent, C., Goikolea, J.M., Banús, S., Salamero, M., 2002. [Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale]. Med Clin (Barc) 119, 366–71.

Corponi, F., Anmella, G., Verdolini, N., Pacchiarotti, I., Samalin, L., Popovic, D., Azorin, J.M., Angst, J., Bowden, C.L., Mosolov, S., Young, A.H., Perugi, G., Vieta, E., Murru, A., 2020. Symptom networks in acute depression across bipolar and major depressive disorders: A network analysis on a large, international, observational study. Eur Neuropsychopharmacol 35, 49–60. https://doi.org/10.1016/J.EURONEURO.2020.03.017

Corponi, F., Li, B.M., Anmella, G., Mas, A., Sanabra, M., Vieta, E., Group, I., Lawrie, S.M., Whalley, H.C., Hidalgo-Mazzei, D., Vergari, A., 2023. Automated mood disorder symptoms monitoring from multivariate time-series sensory data: Getting the full picture beyond a single number. medRxiv 2023.03.25.23287744. https://doi.org/10.1101/2023.03.25.23287744

Critchley, H.D., 2002. Review: Electrodermal Responses: What Happens in the Brain. The Neuroscientist 8, 132–142. https://doi.org/10.1177/107385840200800209

de Looff, P., Duursma, R., Noordzij, M., Taylor, S., Jaques, N., Scheepers, F., de Schepper, K., Koldijk, S., 2022. Wearables: An R Package With Accompanying Shiny Application for Signal Analysis of a Wearable Device Targeted at Clinicians and Researchers. Front Behav Neurosci 16. https://doi.org/10.3389/FNBEH.2022.856544

De Prisco, M., Oliva, V., Fico, G., Fornaro, M., de Bartolomeis, A., Serretti, A., Vieta, E., Murru, A., 2022. Defining clinical characteristics of emotion dysregulation in bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 142, 104914. https://doi.org/10.1016/J.NEUBIOREV.2022.104914

Empatica, 2022. Empatica E4 [WWW Document]. URL https://www.empatica.com/en-gb/research/e4/ (accessed 5.23.22).

Fagiolini, A., Cuomo, A., 2023. Treating major depressive disorder with mixed features. Eur Neuropsychopharmacol 69, 58–59. https://doi.org/10.1016/J.EURONEURO.2023.01.004

Faurholt-Jepsen, M., Kessing, L.V., Munkholm, K., 2017. Heart rate variability in bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 73, 68–80. https://doi.org/10.1016/j.neubiorev.2016.12.007

Föll, S., Maritsch, M., Spinola, F., Mishra, V., Barata, F., Kowatsch, T., Fleisch, E., Wortmann, F., 2021. FLIRT: A feature generation toolkit for wearable data. Comput Methods Programs Biomed 212, 106461. https://doi.org/10.1016/J.CMPB.2021.106461

Fusar-Poli, P., Manchia, M., Koutsouleris, N., Leslie, D., Woopen, C., Calkins, M.E., Dunn, M., Tourneau, C. Le, Mannikko, M., Mollema, T., Oliver, D., Rietschel, M., Reininghaus, E.Z., Squassina, A., Valmaggia, L., Kessing, L.V., Vieta, E., Correll, C.U., Arango, C., Andreassen, O.A., 2022. Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. Eur Neuropsychopharmacol 63, 17–34. https://doi.org/10.1016/J.EURONEURO.2022.08.001

Greco, A., Valenza, G., Lanata, A., Rota, G., Scilingo, E.P., 2014. Electrodermal activity in bipolar patients during affective elicitation. IEEE J Biomed Health Inform 18, 1865–1873. https://doi.org/10.1109/JBHI.2014.2300940

Hamilton, M., 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23, 56–62.

Hausberg, M., Hillebrand, U., Kisters, K., 2007. Addressing sympathetic overactivity in major depressive disorder. J Hypertens 25, 2004–2005. https://doi.org/10.1097/HJH.0B013E3282EF9819

Hsin, H., Fromer, M., Peterson, B., Walter, C., Fleck, M., Campbell, A., Varghese, P., Califf, R., 2018. Transforming Psychiatry into Data-Driven Medicine with Digital Measurement Tools. NPJ Digit Med 1, 37. https://doi.org/10.1038/s41746-018-0046-0

Iacono, W.G., Lykken, D.T., Peloquin, L.J., Lumry, A.E., Valentine, R.H., Tuason, V.B., 1983. Electrodermal Activity in Euthymic Unipolar and Bipolar Affective Disorders: A Possible Marker for Depression. Arch Gen Psychiatry 40, 557–565. https://doi.org/10.1001/archpsyc.1983.01790050083010

Ilzarbe, L., Vieta, E., 2023. The elephant in the room: Medication as confounder. European Neuropsychopharmacology 71, 6–8. https://doi.org/10.1016/J.EURONEURO.2023.03.001

Imbault, C., Kuperman, V., 2018. Emotional reactivity and perspective-taking in individuals with and without severe depressive symptoms. Scientific Reports 2018 8:1 8, 1–8. https://doi.org/10.1038/s41598-018-25708-x

Johnson, K.T., Picard, R.W., 2020. Advancing Neuroscience through Wearable Devices. Neuron 108, 8–12. https://doi.org/10.1016/j.neuron.2020.09.030

Li, B.M., Corponi, F., Anmella, G., Mas, A., Sanabra, M., Hidalgo-Mazzei, D., Vergari, A., 2022. Inferring mood disorder symptoms from multivariate time-series sensory data.

Miller, C.J., Johnson, S.L., Eisner, L., 2009. Assessment Tools for Adult Bipolar Disorder. Clin Psychol (New York) 16, 188. https://doi.org/10.1111/J.1468-2850.2009.01158.X

Moretta, T., Kaess, M., Koenig, J., 2023. A comparative evaluation of resting state proxies of sympathetic and parasympathetic nervous system activity in adolescent major depression. J Neural Transm (Vienna) 130, 135–144. https://doi.org/10.1007/S00702-022-02577-3

Orsolini, L., Fiorani, M., Volpe, U., 2020. Digital Phenotyping in Bipolar Disorder: Which Integration with Clinical Endophenotypes and Biomarkers? Int J Mol Sci 21, 1–21. https://doi.org/10.3390/IJMS21207684

Pacchiarotti, I., Anmella, G., Colomer, L., Vieta, E., 2020. How to treat mania. Acta Psychiatr Scand 142, 173–192. https://doi.org/10.1111/acps.13209

Posada-Quintero, H.F., Chon, K.H., 2020. Innovations in Electrodermal Activity Data Collection and Signal Processing: A Systematic Review. Sensors (Basel) 20. https://doi.org/10.3390/S20020479

Posada-Quintero, H.F., Florian, J.P., Orjuela-Cañón, Á.D., Chon, K.H., 2016. Highly sensitive index of sympathetic activity based on time-frequency spectral analysis of electrodermal activity. Am J Physiol Regul Integr Comp Physiol 311, R582–R591. https://doi.org/10.1152/AJPREGU.00180.2016

Ramos-Brieva, J.A., Cordero-Villafafila, A., 1988. A new validation of the Hamilton Rating Scale for Depression. J Psychiatr Res 22, 21–8.

Sarchiapone, M., Gramaglia, C., Iosue, M., Carli, V., Mandelli, L., Serretti, A., Marangon, D., Zeppegno, P., 2018. The association between electrodermal activity (EDA), depression and suicidal behaviour: A systematic review and narrative synthesis. BMC Psychiatry 18. https://doi.org/10.1186/s12888-017-1551-4

Setz, C., Arnrich, B., Schumm, J., La Marca, R., Tröster, G., Ehlert, U., 2010. Discriminating stress from cognitive load using a wearable EDA device. IEEE Trans Inf Technol Biomed 14, 410–417. https://doi.org/10.1109/TITB.2009.2036164

Swann, A.C., Secunda, S.K., Koslow, S.H., Katz, M.M., Bowden, C.L., Maas, J.W., Davis, J.M., Robins, E., 1991. Mania: Sympathoadrenal function and clinical state. Psychiatry Res 37, 195–205. https://doi.org/10.1016/0165-1781(91)90075-Z

Taylor, S., Jaques, N., Chen, W., Fedor, S., Sano, A., Picard, R., 2015. Automatic identification of artifacts in electrodermal activity data. Annu Int Conf IEEE Eng Med Biol Soc 2015, 1934–1937. https://doi.org/10.1109/EMBC.2015.7318762

Thorell, L.H., Wolfersdorf, M., Straub, R., Steyer, J., Hodgkinson, S., Kaschka, W.P., Jandl, M., 2013. Electrodermal hyporeactivity as a trait marker for suicidal propensity in uni- and bipolar depression. J Psychiatr Res 47, 1925–1931. https://doi.org/10.1016/J.JPSYCHIRES.2013.08.017

Tohen, M., Frank, E., Bowden, C.L., Colom, F., Ghaemi, S.N., Yatham, L.N., Malhi, G.S., Calabrese, J.R., Nolen, W.A., Vieta, E., Kapczinski, F., Goodwin, G.M., Suppes, T., Sachs, G.S., Chengappa, K.R., Grunze, H., Mitchell, P.B., Kanba, S., Berk, M., 2009. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 11, 453–473. https://doi.org/10.1111/j.1399-5618.2009.00726.x

Van Assche, E., Antoni Ramos-Quiroga, J., Pariante, C.M., Sforzini, L., Young, A.H., Flossbach, Y., Gold, S.M., Hoogendijk, W.J.G., Baune, B.T., Maron, E., 2022. Digital tools for the assessment of pharmacological treatment for depressive disorder: State of the art. Eur Neuropsychopharmacol 60, 100–116. https://doi.org/10.1016/J.EURONEURO.2022.05.007

van Lier, H.G., Pieterse, M.E., Garde, A., Postel, M.G., de Haan, H.A., Vollenbroek-Hutten, M.M.R., Schraagen, J.M., Noordzij, M.L., 2020. A standardized validity assessment protocol for physiological signals from wearable technology: Methodological underpinnings and an application to the E4 biosensor. Behav Res Methods 52, 607–629. https://doi.org/10.3758/S13428-019-01263-9/TABLES/7

Vasudevan, S., Saha, A., Tarver, M.E., Patel, B., 2022. Digital biomarkers: Convergence of digital health technologies and biomarkers. npj Digital Medicine 2022 5:1 5, 1–3. https://doi.org/10.1038/s41746-022-00583-z

Vieta, E., 2015. La medicina personalizada aplicada a la salud mental: la psiquiatría de precisión. Rev Psiquiatr Salud Ment 8, 117–118. https://doi.org/10.1016/j.rpsm.2015.03.003

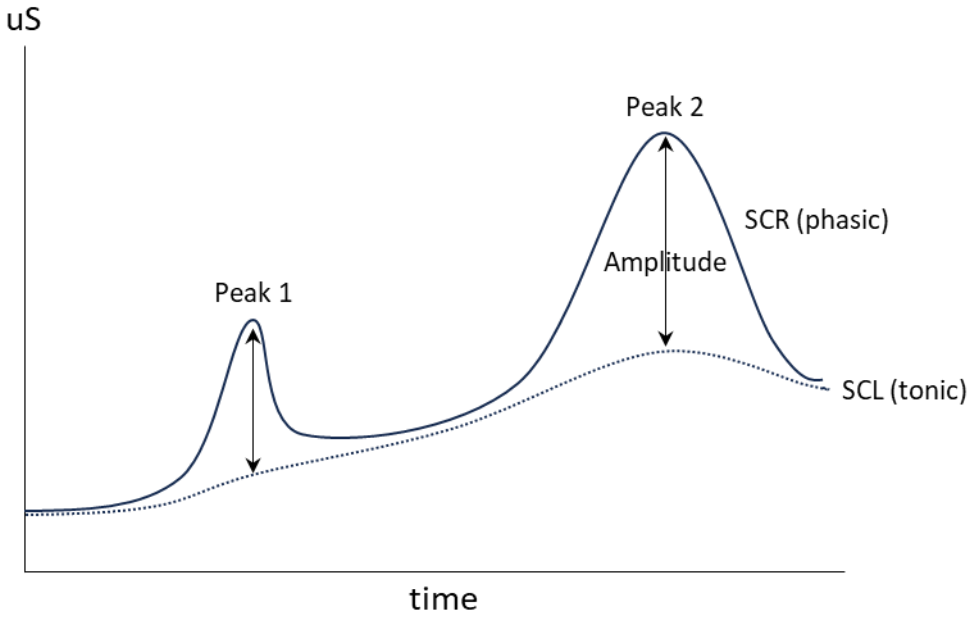
Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., Gao, K., Miskowiak, K.W., Grande, I., 2018. Bipolar disorders. Nature Reviews Disease Primers 2018 4:1 4, 1–16. https://doi.org/10.1038/nrdp.2018.8

Williams, K.M., Iacono, W.G., Remick, R.A., 1985. Electrodermal activity among subtypes of depression. Biol Psychiatry 20, 158–162. https://doi.org/10.1016/0006-3223(85)90075-7

Wolfersdorf, M., Straub, R., Barg, Th., Keller, F., 1996. Depression und EDA-Kennwerte in einem Habituationsexperiment. Fortschritte der Neurologie · Psychiatrie 64, 105–109. https://doi.org/10.1055/s-2007-996376

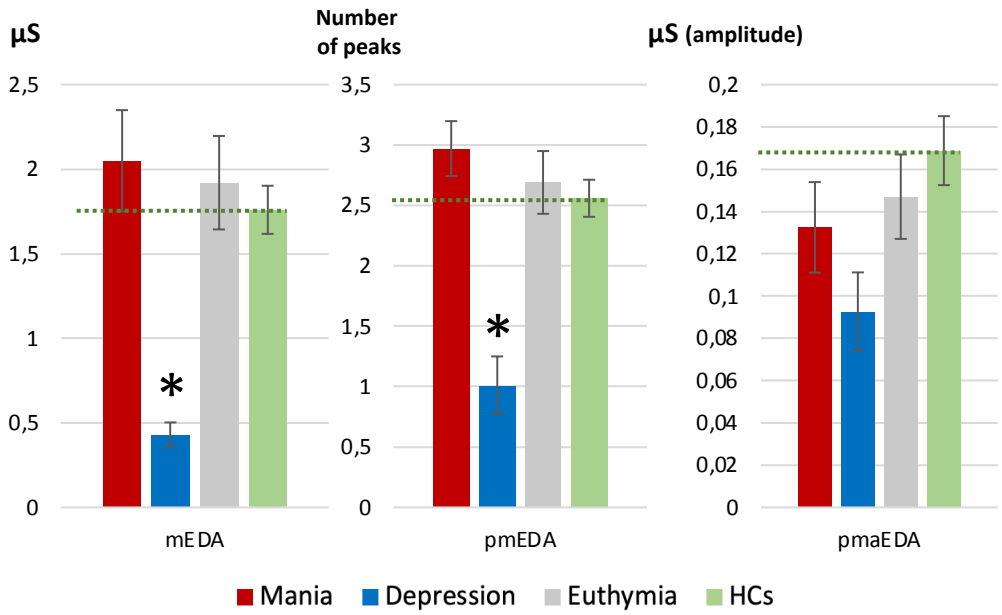
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133, 429–35.

Figure 1. EDA signal simplistic representation of phasic and tonic components.



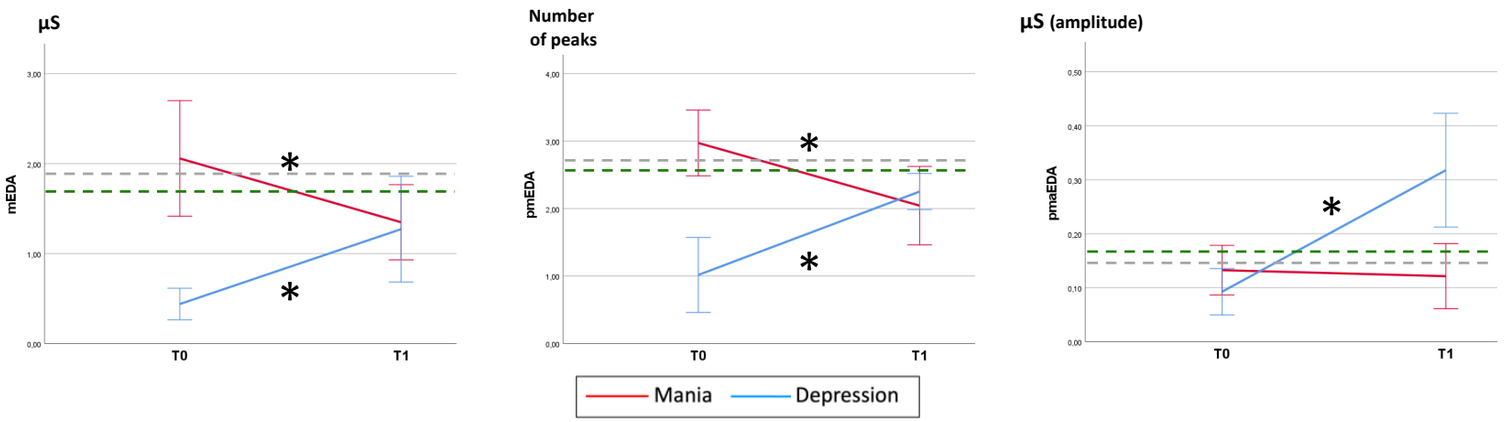
The figure represents an EDA longitudinal register with two peaks. Each peak has its amplitude (arrow) and corresponds to the phasic activity or skin conductance response (SCR). Dashed line represents the tonic activity or skin conductance conductance level (SCL).

Figure 2. Inter-subject comparisons of EDA parameters.



*The figure shows inter-subject comparisons of EDA parameters. Error bars represent the standard error of the mean. Dashed bars represent the mean values for healthy controls, as a measure reference for comparability between mood states. * p<0.05*

Figure 3. EDA parameters´ differences in manic and depressed bipolar patients before and after response to treatment.



Error bars: CI 95%

The figure shows intra-subject longitudinal comparisons of EDA parameters during acute mood episodes (T0) and at clinical remission (T1). Error bars represent the standard error of the mean. Grey dashed bars represent the mean values for BD patients at euthymia and green dashed bars for healthy controls, as reference measures for comparability between mood states. p<0.05*

Table 1. Participant´s sociodemographic and medical history

		Bipolar disorder (n=49)		Healthy controls (n=19)			
		Mean	**SD**	**Mean**	**SD**	**t**	**p**
Age		47	14	40	15	1.890	0.063
		N	**%**	**N**	**%**	**χ2**	**p**
Sex	Female	27	55.1%	13	68.4%	1	0.316
	Male	22	44.9%	6	31.6%		
Medical comorbidity		21	42.9%	4	21.0%	2.8	0.094

Table 2. Patients with bipolar disorder: clinical characteristics and longitudinal affective symptoms' scores

		Mania (n=15)		Depression (n=9)		Euthymia (n=25)			
		N	%	N	%	N	%	χ^2	p
Sex	Female	8	53%	6	67%	13	52%	0.60	0.74
	Male	7	47%	3	33%	12	48%		
Medical comorbidity		6	40%	3	33%	12	48%	0.65	0.72
BD type	Type 1	15	80%	5	56%	15	60%	2.9	0.57
	Type 2	0	20%	4	44%	9	36%		
	NOS	0	0%	0	0%	1	4%		
History of SUD	Multiple	5	33%	0	0%	1	4%	17.3	0.008
	None	7	47%	7	78%	23	92%		
	Cannbis	3	20%	1	11%	1	4%		
	Alcohol	0	0%	1	11%	0	0%		
Psychotic symptoms		9	60%	0	0%	0	0%	25	0.001
		Mean	SD	Mean	SD	Mean	SD	F	p
Age		41.0	13.6	45.1	13.6	51.3	13.4	2.82	0.07
Illness years		6.6	7.7	17.1	11.3	13.8	8.9	3.23	0.049
YMRS score	T0	26.8	4.7	1.6	1.4	1	1		
	T1	3.7	4.3	2.2	3.4	NA	NA		
HDRS score	T0	5.3	3.0	18.4	4.7	2.0	1.0		
	T1	3.7	2.1	3.9	2.1	NA	NA		

YMRS = Young Mania rating scale

HDRS = 17-item Hamilton Depression rating scale

NOS = Not otherwise specified

SUD = Substance use disorder

NA = Not applicable