European Archives of Psychiatry and Clinical Neuroscience (2019) 269:761–775
https://doi.org/10.1007/s00406-018-0935-x

ORIGINAL PAPER

Bipolar disorder in the balance

Brian J. Lithgow[1,2] · Zahra Moussavi[2] · Caroline Gurvich[1] · Jayashri Kulkarni[1] · Jerome J. Maller[1] · Paul B. Fitzgerald[1]

Received: 17 December 2017 / Accepted: 30 July 2018 / Published online: 6 August 2018

Abstract

Bipolar disorder (BD) is a severe mood disorder that lacks established electrophysiological, neuroimaging or biological markers to assist with both diagnosis and monitoring disease severity. This study's aim is to describe the potential of new neurophysiological features assistive in BD diagnosis and severity measurement utilizing the recording of electrical activity from the outer ear canal called Electrovestibulography (EVestG). From EVestG data sensory vestibulo-acoustic features were extracted from a single supine-vertical translation stimulus to distinguish 50 depressed and partly remitted/remitted bipolar disorder patients [18 symptomatic (BD-S, MADRS > 19), 32 reduced symptomatic (BD-R, MADRS ≤ 19)] and 31 age and gender matched healthy individuals (controls). Six features were extracted from the measured firing pattern interval histogram and the extracted shape of the average field potential response. Five of the six features had low but significant correlations ($p < 0.05$) with the MADRS assessment. Using leave-one-out-cross-validation, unbiased parametric and non-parametric classification routines resulted in 75–79%, 84–86%, 76–85% and 79–82% accuracy for separation of control from BD, BD-S and BD-R as well as BD-S from BD-R groups, respectively. The main limitation of this study was the inability to fully disentangle the impact of prescribed medication from the responses recorded. A mix of stationary and movement evoked EVestG features produced good discrimination between control and BD patients whether BD-S or BD-R. Moreover, BD-S and BD-R appear to have measurably different pathophysiological manifestations. The firing pattern features used were dissimilar to those observed in a prior major depressive disorder study.

Keywords Bipolar disorder · Depression · Neurobiology · Electrovestibulography · Biological markers · Vestibular

Abbreviations

AD	Antidepressant medication
AMPA	a-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Background phase	1.5 s EVestG recording immediately prior to motion
BD	Bipolar disorder, (-S) symptomatic, (-R) reduced symptomatic (-R can be broken into (-M) mild and (-A) asymptomatic)
EVestG	Electrovestibulography
FP	Field potential
IH1, IH2	EVestG short interval features. Intervals were the time between detected FP's
IH331, IH332	EVestG long interval features. Intervals were the time between each 33rd FP
LDA	Linear discriminant analysis
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major depressive disorder, (-S) symptomatic, (-R) reduced symptomatic
MS	Mood stabilizer medication
NDMA	*N*-methyl-D-aspartate
AP	Antipsychotic medication

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00406-018-0935-x) contains supplementary material, which is available to authorized users.

✉ Brian J. Lithgow
Brian.Lithgow@umanitoba.ca; Brian.Lithgow@monash.edu

[1] Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred Hospital, 607 St Kilda Rd, Melbourne, VIC, Australia

[2] Diagnostic and Neurosignal Processing Research Laboratory, Riverview Health Centre, University of Manitoba, Winnipeg, MB, Canada

NEER	Neural event extraction routine
NM	No-medication
NPC	Non-parametric classifier
Acceleration phase	1.5 s EVestG recording during the acceleration phase
Deceleration phase	1.5 s EVestG recording during the deceleration phase
Sh1, Sh2	EVestG shape features

Introduction

Bipolar disorder (BD) is classically described as clinically significant periods of depression and/or (hypo)mania. BD is a severe mood disorder that lacks established electrophysiological, neuroimaging or biological markers to assist with both diagnosis and monitoring disease severity. Up to 40% of BD (and more particularly type II BD) patients are initially misdiagnosed with major depressive disorder (MDD) [1, 2]. Correct diagnosis of BD (particularly type II) from MDD can take the order of years if the predominant disease polarity is depressive [3]. This study describes the potential of new neurophysiological features for BD diagnosis and severity measurement utilizing the recording of electrical activity from the outer ear canal called Electrovestibulography (EVestG). This and our previous MDD study [4] will ultimately target the need [5] for biomarkers to separate MDD and BD in their depressive phase.

To establish the relationship between BD and the vestibulo-acoustic response (recorded by EVestG) we briefly describe the impact of BD on both the vestibular and acoustic systems.

BD and the vestibular

There are a number of substantial neurobiological links between the brain processes regulating vestibular activity in the brainstem and brain regions implicated in the neurobiology of BD; this suggests the potential use of the assessment of vestibular responses in this disorder [6]. The mammalian efferent vestibular system is spontaneously active [7], and able to effect peripheral afferent responses. The Efferent Vestibular System receives input from peripheral afferents [8], the Vestibular Nucleus bilaterally [9] and other (e.g., somatosensory [7]) systems. The Vestibular Nucleus receives substantial input from several brain regions [10] broadly implicated in the pathophysiology of BD including the Locus Coeruleus, Dorsal Raphe and Parabrachial nuclei [6]. The Locus Coeruleus, amygdala and hypothalamus are BD-relevant regions; the Parabrachial Nucleus, for example, has reciprocal connections with the Locus Coeruleus, amygdala and hypothalamus (Supplement: Vestibular Connectivity) [6, 10]. Structural, throughput and/or metabolic change in the Dorsal Raphe Nuclei, Parabrachial Nucleus and Locus Coeruleus (primary sources of norepinephrine/acetylcholine/serotonin) occur that will have wide ranging and complex effects including providing multiple potential pathways for change of vestibular (nucleus) response in those participants with BD. The Vestibular Nucleus then connects to the Efferent Vestibular System providing a potential path to influence peripheral vestibular responses. Based on these connections, the vestibular system has been suggested as a potential window for exploring psychiatric symptomology [6].

BD and the auditory

Psychiatric medications, such as lithium, are known to potentiate auditory responses [11]. With the exceptions of hyperacusis and tinnitus, overall, there is a scarcity of a substantial body of definitive evidence that the auditory system is significantly impacted by the onset of a psychiatric illness. For example, no link has been found between the neuropathology of the superior olivary nucleus and schizophrenia or auditory hallucinations [12]. Additionally, psychogenic hearing loss, e.g., pseudohypacusis, is without evidence of organic cause [13]. Whilst the notion of emotional stress as a modulator of the auditory system is novel [14] chronic stress exposure seems to be harmful to hearing [15].

In tinnitus patients, a recent review shows the prevalence of psychiatric disorders, particularly anxiety and depression, is high; also, the presence of these disorders correlates with tinnitus-related annoyance and severity [16]. Hyperacusis is frequently comorbid with migraine (7–12%), tinnitus (24–44%), depression (17–23%) and anxiety (10–23%, generalized anxiety disorder and post-traumatic stress disorder) [17]. Migraine involves serotonin pathways, and has been postulated to be one of the root causes of central hyperacusis [18]. Antidepressants and anti-anxiety medications can be used to deal with the psychological fallout from hyperacusis but often only with marginal success. There are many psychiatric patients with hyperacusis or hypoacusis, often with normal audiograms, suggestive that, overall, psychiatric disorders have minimal impact on organic hearing loss. However, the evidence is supportive of a mechanism by which the acoustic response may be modulated by anxiety and/or depression.

Previous EVestG studies

Electrovestibulography (EVestG) detects specific vestibulo-acoustic and more particularly vestibular field potentials (FP's) [19, 20] (Supplement: Comparison of Acoustic and Vestibular Spontaneous activities) potentially providing a quantitative indirect measure of activity in brain regions and neural pathways frequently compromised in neuropsychiatric

disease. A vestibular driven (brainstem and periphery) response, stimulated by a whole body passive movement using a computer-controlled hydraulic tilt chair/table with a sinusoidal velocity profile, is measured in EVestG recordings [19] (Fig. 1a, e). Recently, EVestG recordings have been applied to post-concussion syndrome [21], Parkinson's disease [22] and Meniere's disease [23] for measuring drug effects, symptomatology or in classification. In addition, we showed significantly altered EVestG measured responses in persons with MDD as compared to healthy controls [4].

This study aims to investigate whether depressed and euthymic BD individuals would manifest an altered vestibulo-acoustic (predominantly vestibular) response to passive movement stimuli, and if they did, whether the abnormal activity could have properties consistent with an illness specific feature (biomarker). We hypothesized that depressed and euthymic BD individuals would have significantly altered vestibular responses compared to those of healthy individuals, and also that the degree of alteration in vestibular activity would relate to illness severity. We investigated our hypotheses by measuring vestibular responses using EVestG [19] in a group of depressively symptomatic BD (BD-S) and a group of BD participants in remission or with mild depressive residual symptoms (BD-R) and also in a group of age-and gender matched healthy individuals.

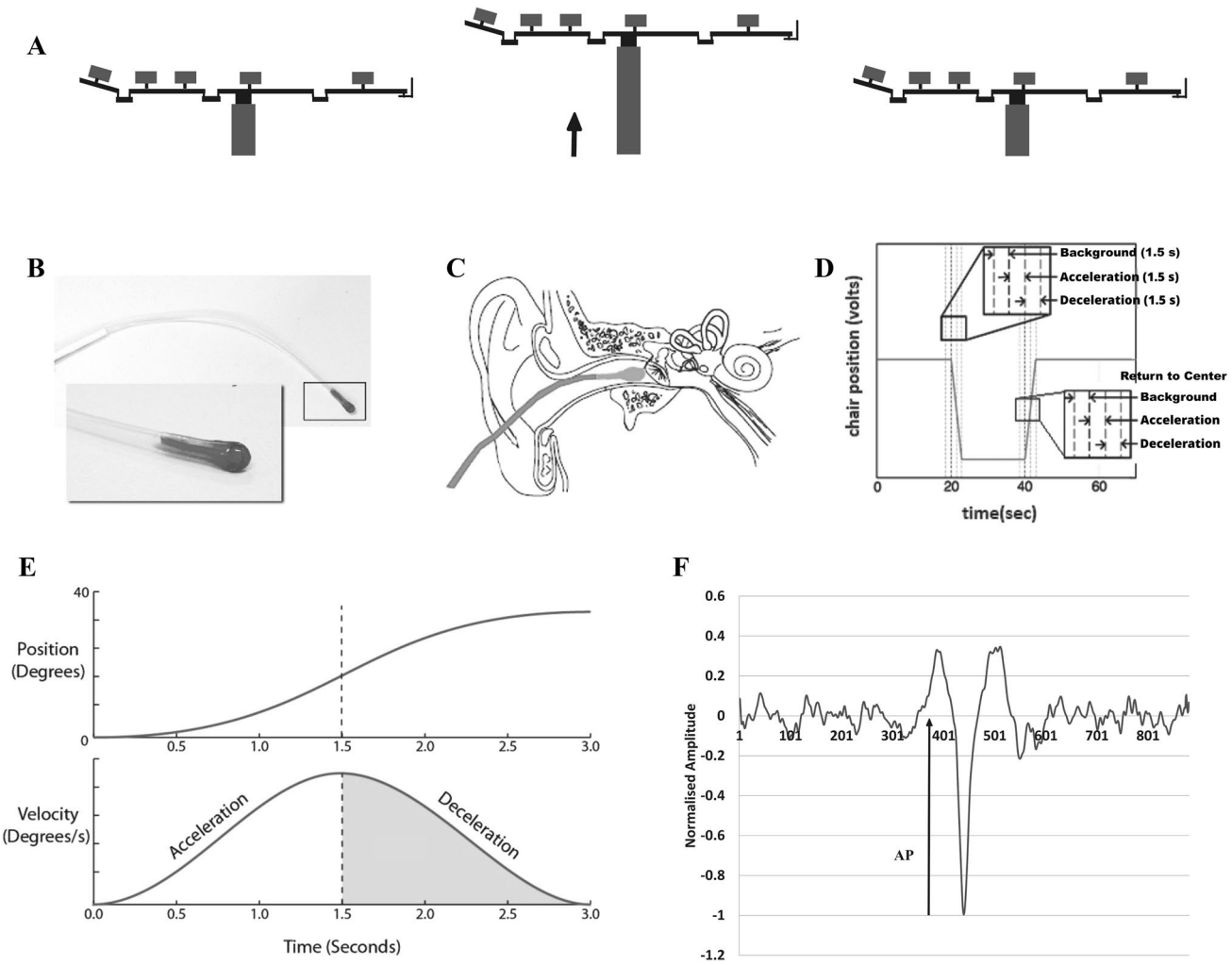

Fig. 1 EVestG Methodology. **a** EVestG table translation; **b** ear canal electrode TM-EcochGtrode (Bio-logic, France); **c** ear canal electrode placement, reference electrodes were placed on the ipsilateral earlobes and a common ground electrode placed on the forehead; **d** Translation movement phase definitions; **e** position and velocity profiles during translation for each inset in **d** and; **e** example averaged field potential (FP) [horizontal scale is in samples (41.67 kHz)]. From [4] with permission, Taylor & Francis, http://www.tandfonline.com

Methods and materials

Participants

Fifty individuals (28 males) with a current clinical DSM-IV diagnosis of BD type I or II (confirmed by study psychiatrist PF or JK) and without any other psychiatric or neurological disorder (confirmed by their treating psychiatrist) and 31 healthy age and gender matched healthy individuals (as controls) who had undergone exclusion tests (including the Mini-International Neuropsychiatric Interview screening tool and the Mini Mental State Examination) for psychiatric illness participated in the study. Mania was assessed using the Young Mania Rating Scale (YMRS) and those with a score ≥ 14 were priorly excluded from this study. The Montgomery Asberg Depression Rating Scale (MADRS) [24] was used to quantify the severity of depression at the time of testing. Of the 50 BD participants 18 were labelled "symptomatic" (BD-S) suffering moderate to severe depression (MADRS ≥ 20) and 32 were labelled "reduced symptomatic" [BD-R, of which 16 presented in remission from depression (asymptomatic, MADRS ≤ 6) and 16 presented with mild depression (MADRS 7–19)]. Two included BD subjects were identified with ADHD using the Adult ADHD self-reporting scale. The presence of anxiety in BD subjects (including generalized anxiety disorder, social or specific phobias, PTSD, or panic disorder) was determined ($N = 23$) from the Mini-International Neuropsychiatric Interview assessment. Both BD participants and controls were given a screening hearing test. No BD patients or controls analyzed in this study reported the presence of migraine, tinnitus or hyperacusis. Two BD-R participants were not on antipsychotic, antidepressant or mood stabilizer medications at the time of testing. Table 1 shows the average demographic information of the participants (Supplement: Detailed Patient Demographics, Table S1).

EVestG signals were recorded from participates with closed eyes and in a relaxed state in a supine position with their neck supported (to minimize artefacts) on a hydraulic chair inside an electromagnetically shielded and sound attenuated (> 30 dB) chamber. A gelled electrode consisting of a wick (Fig. 1b) was positioned to rest close to the tympanic membrane (Fig. 1c) of each ear. A supine vertical translation/movement (producing predominantly utricular stimulation) was selected as that produces the largest vestibular response [25] with least artefact. Recordings were made during the downward part of a 15 cm vertical translation. The movement was repeated twice and data of the second stimulation recorded; the first was for participant familiarization. During the measurement, the subject remained passive with closed eyes, and was not required to interact cognitively.

Recording were made whilst the chair was stationary (static) and moving (dynamic). The background region (1.5 s of background recording immediately prior to chair's movement) (Fig. 1d) was considered as the static phase response (Supplement: Background segment selection). The 1.5 s acceleration and deceleration regions of Fig. 1d, e were considered as the dynamic response phases.

To produce an average FP plot (e.g., Fig. 1f), the Neural Event Extraction Routine (NEER) [19] averages the detected spontaneous and driven FPs (Supplement: NEER) and generates an interval histogram of the FP occurrences.

EVestG feature extraction

The recorded EVestG response can only vary in FP shape or firing pattern. To enable BD classification and severity measurement these measures were recorded and analyzed to

Table 1 BD and control study participant demographics and psychiatric assessments (BD-R = BD-A and BD-M)

	Diagnosis	Anxiety	Sex	Age	Years since diagnosis	MMSE total	MADRS	YMRS
AVG	Control $n = 31$		12M	39.97		29.40	1.77	
STDEV				15.63		1.02	1.91	
AVG	Asymptomatic, BD-A $n = 16$	$n = 2$	9M	47.88	15.56	28.93	2.75	3.81
STDEV	MADRS ≤ 6			14.65	13.67	1.28	2.05	4.23
AVG	Mild, BD-M $n = 16$	$n = 10$	7M	42.56	13.94	28.80	12.00	3.00
STDEV	All MADRS 7–19			12.42	10.46	1.56	3.54	4.07
AVG	BD-R = (BD-A and BD-M)	$n = 12$	16M	45.22	14.75	28.86	7.38	4.53
STDEV	$n = 32$, all MADRS ≤ 19			13.84	12.20	1.43	5.45	4.32
AVG	BD-S, moderate-severe	$n = 11$	5M	49.82	17.38	28.71	28.65	3.00
STDEV	$n = 18$ MADRS ≥ 20			12.35	10.19	1.36	6.06	4.07
AVG	BD (BD-R and BD-S)	$n = 23$	21M	46.82	15.66	28.80	14.76	4.00
STDEV	$n = 50$, all MADRS			13.66	11.73	1.42	11.73	4.34

derive three reflective feature types (below). These EVestG feature types were those used in the identification of MDD subjects from healthy controls (as well as MDD-S from MDD-R groups) [4]. Where a derived feature was made up of components (e.g., more than one area of the FP curve) each of the components as well as the entire derived feature was tested to ensure robustness of the significance of the selected region using 10-fold-cross-validation. Using the derived features, classification was performed using linear discriminant analysis (LDA) and a Non-Parametric Classifier (NPC) using a leave-one-out-cross-validation analysis (to remove training bias), wherein each left-out subject's data was classified to belong to one of two groups. SPSS Version 22 software (IBM, New York, NY, USA) was used for statistical analysis. Statistical significance (p value) was set at 0.05 unless specified.

The study was approved by The Alfred Human Ethics Committee (Approval number 95/06); therefore, the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki, and all participants gave written consent prior to the experiments.

Results

Feature extraction

Shape features

Figure 2 shows the normalized shape of the extracted average FP during the background static phase (no movement and using a leave-one-out routine) for each BD group (BD, BD-S and BD-R) versus controls and between BD-S and BD-R groups. Average data for control versus the BD groups and BD-S versus BD-R were found to have significant differences useful in characterizing populations. The FP region(s) with statistically significant difference between the average BD and control group responses were determined (Fig. 2a). After examining each significant region for robustness using tenfold-cross-validation the 95% significantly different and robust left-hand side post-potential trough (PPT) regions (see Fig. 2a for region definitions) were used to form the shape feature Sh1 (details Table 2a). For each test subject's average FP (which was the leave-one-out data in the leave-one-out routine), we found two correlation coefficients (one with the BD and one with the control group); the difference between these two coefficients was selected as a Sh1. These 95% confident different regions are suggestive of repolarization mechanisms being affected.

As separation of BD-S and BD-R groups was also an objective, FP shape differences between BD-S and BD-R were examined. There is evidence that left right vestibular response asymmetry is observed in depression and that dynamic responses may be impacted [26, 27]. Dynamic (acceleration phase) asymmetries between right and left responses were observed as significantly different between BD-S and BD-R populations (Fig. 2b). The Sh2 feature formation process, which is based on this observation, is shown in Fig. 2b. To form this feature: the left and right BD-S acceleration responses were subtracted to form BD-S (left minus right); the BD-R responses were similarly subtracted to form BD-R (left minus right) and; the two left minus right responses subtracted to form the black trace in the middle of Fig. 2b. Feature Sh2 was derived from the 95% significant different grey shaded areas of Fig. 2b (details in Table 2a). These areas occur in the pre-potential trough (pre-PT), post-potential peak (PPP) and brainstem (BS) regions (Fig. 2). For each test subject's average FP (which was the leave-one-out data in the leave-one-out routine), we found two correlation coefficients (one with the BD-S (left–right) and one with the BD-R (left–right) group); the difference between these two coefficients was selected as feature Sh2. Also indicated is a blue shaded area wherein BD-S and control (dotted blue curve) are 95% confident different.

The pre-potential peak and post-potential peak regions are suggestive of both depolarization (Na^+) and repolarization (K^+) mechanisms, respectively, being affected. Interestingly, the post-potential peak region (P1 of the acoustically derived Compound action-potential) is shown to be derived peripherally whereas the post-potential trough region (N2) is likely a combination of peripheral and brainstem response activity [28]. As features like Sh2 also had a significant difference region well after the post-potential trough region; by inference this is suggestive of a predominantly brainstem influence.

Small window interval histogram features (IH)

Using the NEER algorithm [19], the time of occurrence of each detected FP was recorded and the time intervals between successive FPs was plotted to form an interval histogram (IH). The IH consisted of 25 logarithmically spaced bins spanning 1.4–22 ms. This was generated during the background static phase (no movement) and compared between average BD-S and BD-R groups on both the right (Fig. 3a) and left (Fig. 3c) sides. In regions where there were significant differences in the average interval histogram bin values (Fig. 3a, c), those normalized bins or bin regions were combined to form the 95% significant different features detailed in Table 2a as features IH1 (right side) and IH2 (left side) (Fig. 3b, d). Bin 4 in Fig. 3a was determined as a non-robust point. The bin combinations were selected to highlight the desired BD-S BD-R group separation (yellow hashes indicate standard error (SE) significance). As the BD-S IH distribution appears right shifted, feature IH2, for example, represents a comparison of low versus

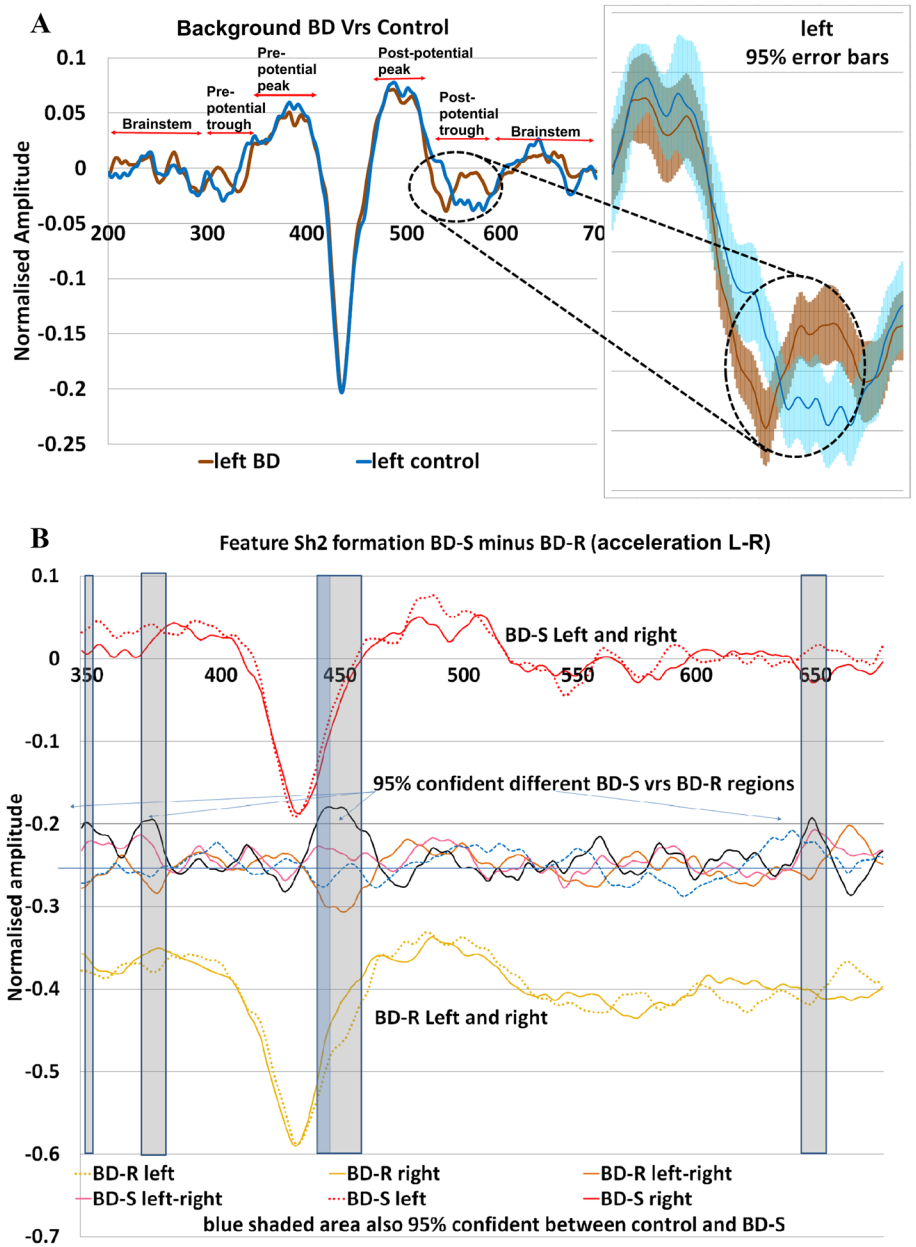

Fig. 2 Shape features Sh1 and Sh2. **a** Left side static (background) average responses plotted for right handed control ($n=27$) and BD ($n=43$) groups. Shaded regions represent 95% confidence intervals. The circled areas show significant difference regions. For Sh1 these occur in the post-potential trough region. Regions defined by red arrows are: pre-potential trough, pre-potential peak, post-potential peak, post-potential trough and brainstem. **b** BD-S and BD-R (right handed subjects) group acceleration response curves recorded on left and right sides are shown in the upper and lower panes. The left and right-side responses were subtracted to form the two-coloured middle pane traces which were then subtracted to form the black left minus right BD-S minus BD-R response which was used in the formation of feature Sh2. Sh2 was formed from the grey shaded 95% significant different regions of this plot. The blue shading is a region of significant control versus BD-S difference

high (range) interval bin distributions. This right shift may indicate a lower level of spontaneous activity is associated with the BD-S group. Additionally, in Fig. 3a purple (red) asterisks indicate SE significant differences between average control and BD-R (BD-S) responses. As indicated in Fig. 3b feature IH1 can also be applied to control versus BD-R discrimination.

Large window interval histogram features (IH33)

Low frequency (~10 Hz) modulations of spontaneous FP interval activity, as hypothesized [4] to occur in response to efferent or α band activity, were searched for. Spontaneous vestibular efferent activity is seen at 10–50 spikes/s [7] and the α band is 8–13 Hz. Average control and BD interval histograms were generated based on every 33rd FP gap (IH33) (see Fig. 4d for methodology). A 33 FP gap corresponds to about 100 ms (10 Hz) and the lower range of any hypothesized potential efferent/α band modulatory burst firing effect as the average experimentally detected gap measured with NEER was ~3.3 ms.

Static (background) and dynamic (acceleration and deceleration) phase IH33's were generated for the falling translational movement (Fig. 4a, e). The control deceleration response is shifted right (longer intervals) relative to the background (static) response (Fig. 4a). In comparison, the BD background and deceleration responses almost overlap. This difference (using bins 111 and 120 in Fig. 4b as bin

Table 2 Feature definitions, classification and correlation results

(a) LDA and NPC features

Feature	Phase, side	Feature range	Origin plot	Medication sensitivity	Classifier impact	Hand	ROC area (R&L) (CTL vrs S&R, S, R) (S vrs R)
Sh1	Background left (L)	Post-potential trough; samples (537:567 + 572:592)	Control Vrs BD Figure 2a, b		N	Y	0.716, 0.681, 0.736 0.514
Sh2	Acceleration L–R	Pre-potential trough, post-potential peak, brainstem; samples (366:386 + 446:460 + 645:658)	BD-S Vrs BD-R Figure 2c, d	MS, AP	N		0.584, 0.780, 0.526 0.799
IH1	Background R	BD-S longer intervals Bins [(1,2,7)-(12,13,16,23:25)]	BD-S Vrs BD-R Figure 3a, b		N		0.610, 0.536, 0.692 0.788
IH2	Background L	BD-S longer intervals Bins [(4:5)-(16:24)]	BD-S Vrs BD-R Figure 3c, d		N		0.523, 0.602, 0.593 0.697
IH331	Background–deceleration L	CTL shorter intervals Bins [(10:11)]	Control Vrs BD-all Figure 4a–d		N		0.708, 0.652, 0.740 0.562
IH332	Acceleration L	CTL shorter intervals Bins (3-5)-(8-10)	Control Vrs BD-S Figure 4e, f	MS	N	Y	0.588, 0.794, 0.528 0.720

(b) Classifier results

	Accuracy LDA Leave-one out cross validation (%)	Group membership [Gp1,Gp1err,Gp2err,Gp2]	*N* (anxiety) Group 1, group 2	Accuracy NPC Leave-one out weighted vote (%)	Three features (feature label)
Control versus BD	77	[22, 9, 10, 40]	31 (0), 50 (24)	75	(Sh1, Sh2, IH331)
(Right handed (RH) only)	76	[18, 9, 8, 35]	27 (0), 43 (21)	79	
Control versus BD-S	86 (Sh2, IH332)	[27, 4, 3, 15]	31 (0), 18 (11)	84	(Sh1, Sh2, IH332)
(RH only)	86 (Sh2, IH332)	[23, 3, 3, 13]	27 (0), 17 (10)	86	
Control versus BD-R	83	[24, 7, 4, 28]	31 (0), 32 (13)	76	(Sh1, IH1, IH331)
(RH only)	85	[21, 6, 2, 24]	27 (0), 26 (11)	76	
BD-S versus BD-R	82 (Sh2, IH332)	[16, 2, 7, 25]	18 (11), 32 (13)	79	(Sh2, IH2, IH332)
(RH only)	79 (Sh2, IH332)	[15, 2, 7, 19]	17 (10), 26 (11)	79	

(c) MADRS correlations (RH or LH, RH only)

MADRS	Sh1	Sh2	IH1	IH2	IH331	IH332
BD and control	**0.266***, **0.278***	**−0.306****, **−0.334****	−0.096, −0.127	−0.013, −0.023	**−0.256***, **−0.260***	**−0.300****, **−0.310****
BD	0.067, 0.005	**−0.454****, **−0.486****	**−0.383****, **−0.365***	−0.141, −0.222	0.007, 0.002	**−0.353***, **−0.310***
BD-S	0.073, 0.043	−0.208, −0.120	**0.543***, **0.554***	0.113, 0.064	−0.227, −0.234	−0.044, −0.100
BD-R	0.172, 0.133	−0.059, −0.136	−0.152, −0.241	0.291, 0.183	−0.137, −0.203	−0.140, −0.198

YMRS correlations

YMRS	Sh1	Sh2	IH1	IH2	IH331	IH332
BD and control	0.210, **0.301***	−0.008, −0.008	0.135, 0.101	0.152, 0.150	**−0.221***, −0.186	0.005, −0.027
BD	0.014, 0.073	0.125, 0.076	0.008, −0.024	0.190, 0.176	−0.046, −0.010	0.167, 0.171
BD-S	0.014, 0.045	−0.027, −0.116	−0.134, −0.129	−0.037, 0.080	−0.161, 0.163	0.085, 0.123
BD-R	−0.007, 0.049	−0.026, −0.122	−0.032, −0.124	0.187, 0.088	0.095, −0.120	0.044, 0.035

(a) Characteristics of linear discriminant analysis (LDA) and non-parametric classifier (NPC) features. Sh1 and Sh2 are shape features. IH1 and IH2 are short window interval histogram features. IH331 and IH332 are long window interval histogram features. AD, AP, MS indicate antidepressant, antipsychotic, and mood stabilizer sensitivity, respectively (see Supplemental File-Medication Effects). Sh2 (MS and AP) and IH332 (MS) features did not overlap between medicated and non-medicated groups. No feature showed enhanced classification (Classifier Impact) with MS, AD or AP medication. Handedness was detected for features Sh1 and IH332. "Y" indicated a sensitivity to the column label. R is right, L is left and RL is right plus left. The background (BGi) response is the 1.5 s recording immediately prior to the movement stimulus. (b) LDA and NPC results as applied to control versus BD, BD-S and BD-R classification as well as BD-S versus BD-R symptomatology. BD refers to BD-S plus BD-R subjects ($n = 50$). [Gp1, Gp1err, Gp2err, Gp2] is, respectively, the group 1 correct, group 1 error, group 2 error, group 2 correct. (c) MADRS non-parametric spearman rho correlations statistics (* indicates $p < 0.05$, ** indicates $p < 0.01$, these significant results are bolded in Tables (c) and (d))

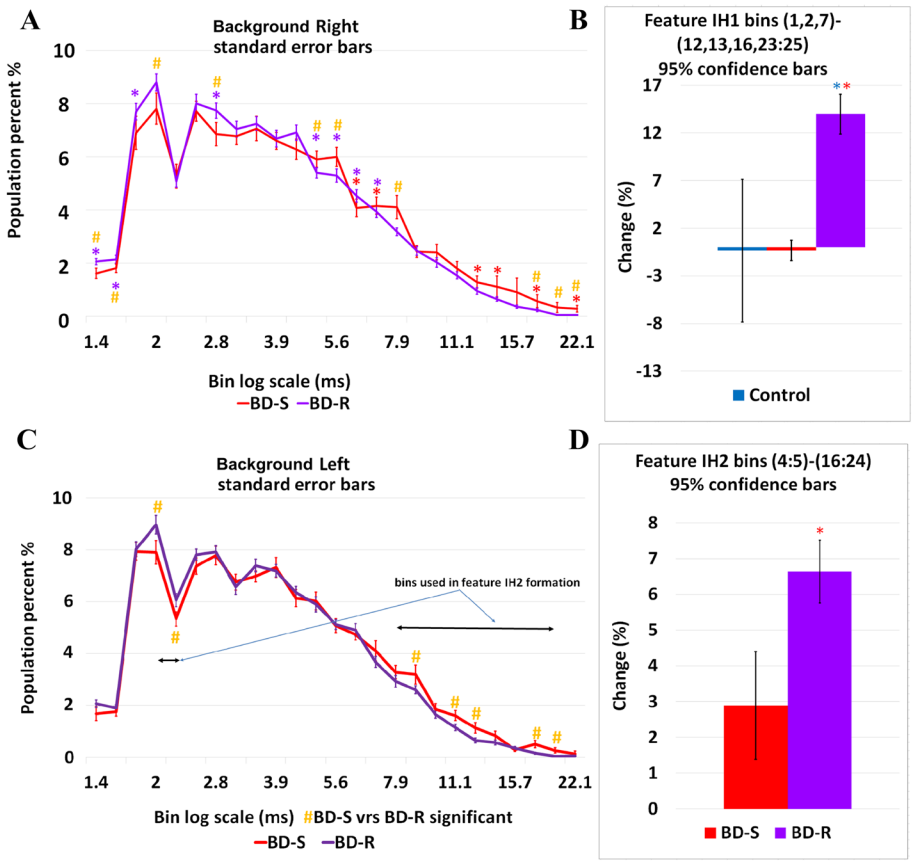

Fig. 3 Interval histograms (IH). **a, c** Right and left side average IH plots for static background recordings for BD-S and BD-R groups. Significant standard error (SE) BD-S versus BD-R difference bins are marked with orange hashes. **b** The significant different bins in pane **a** (excluding bin 4 which was determined as not robust) were combined to amplify, on the right-hand side, the rightward shift observed in the BD-S relative to BD-R response and thus form feature IH1. IH1 was able to produce a 95% significant difference between BD-R and BD-S (or controls). **d** To highlight the right shift of the BD-S relative to BD-R response the left side significant difference bin range 16:24 values were subtracted from bin 4 and 5 values to form feature IH2. IH2 was also able to produce a 95% significant difference between BD-R and BD-S

102 was determined to be non-robust) was used to form the 95% significant feature IH331 of Fig. 4c. The acceleration BD-S response is observed shifted right of the control (and BD-R) acceleration curve for left (Fig. 4e) side responses. That is, there is a longer time gap between the average 33rd BD-S and control (BD-R) group FP gaps. To form the 95% significant different feature IH332 (Fig. 4f) the SE significant short (bins 57:75 ms) and long (102:120 ms) interval bins were subtracted.

Features IH331 and Sh2 may be considered predominantly vestibular response features as much of the common acoustically derived response is likely cancelled out by either the subtraction of left and right or background and deceleration responses [19].

Normalisation

The above extracted features were transformed to a normal distribution where necessary (Supplement: Normalisation). Then, both a Linear Discriminant Analysis [29] and a median based non-parametric classifier (Supplement: NPC classifier) were employed (using SPSS Version 22 or Matlab 2014a) to classify two or more classes of subjects.

Results classification

All combinations ($n \leq 3$) of features were tested for control versus BD, BD-S and BD-R separation and for the ability to separate BD-S and BD-R groups. It was observed that 3-feature combinations could normally provide good group classification accuracy with larger feature combinations only providing marginal improvement.

Classification

Using leave-one-out-cross-validation, unbiased classification routines (LDA and NPC) achieved 75–79%, 84–86%, 76–85% and 79–82% accuracy for separation of control from BD, BD-S and BD-R as well as BD-S from BD-R groups, respectively (Table 2b). Figure 5a shows the 3D plot of the distribution of control versus BD right, left or both handed subjects. The left or both handed subjects present as a cluster on the BD-control border (pink shading) and as a disproportionate number of misclassified BD subjects. Figure 5b shows the improved clustering produced by removing left or both handed subjects from the 3D control versus BD distribution plot. Control versus BD (NPC only), BD-S and BD-R identification was improved by removing left or both handed subjects (Table 2b).

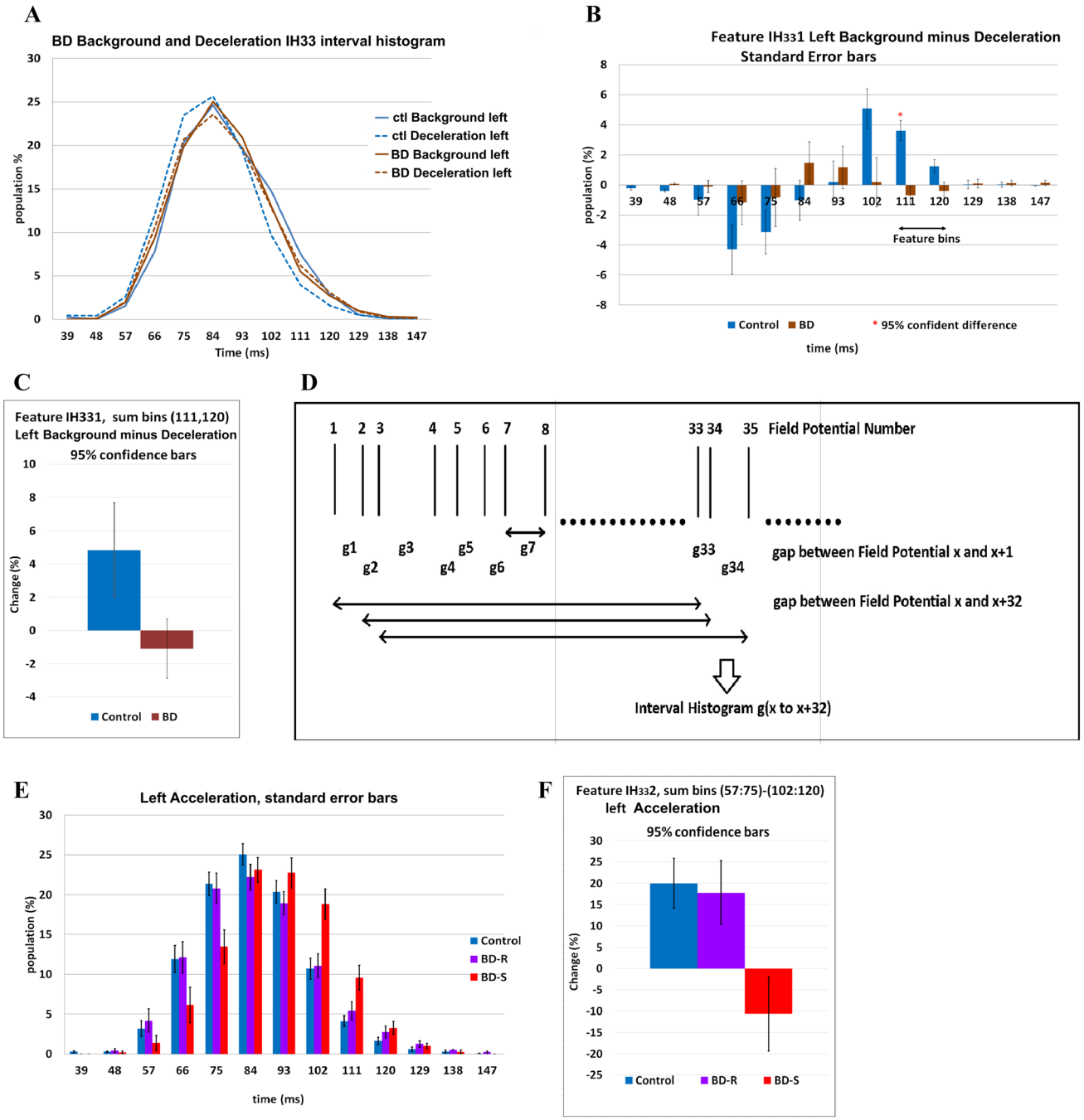

Fig. 4 IH33 features. **a** Left side control and BD background and deceleration phase IH histogram plots for the FP gap equal to 33 (IH33). This IH33 plot consisted of 13 linearly spaced bins spanning 39–147 ms. **b** Feature IH331 was formed by subtracting the deceleration response from the background response. **c** To form feature IH331 bins labelled 111 and 120 were added then IH331 was able to produce a 95% significant difference between controls and BD. **d** The feature IH33 interval histogram generation process. **e** IH33 bin plots for left side acceleration phase responses for control, BD-R and BD-S groups. The BD-S response is shifted right of the control and BD-R plots. **f** The significantly different control and BD-S bins were combined to highlight the right shift and thus form feature IH332 which was able to produce a 95% confidence difference between BD-S and control (and BD-R) groups

Figure 5c, d shows the control versus BD-S and BD-R 3D distribution plots for right handed participants. Figure 5b–d demonstrates significant ($p < 0.01$) separation between control and BD, BD-S and BD-R group means. Identified in the plot are BD subjects with anxiety, left handedness, ADHD and those non-medicated. Features Sh1 and $IH_{33}2$ showed some sensitivity to handedness (Table 2a). Features $IH_{33}2$, IH1 and IH2, in particular,

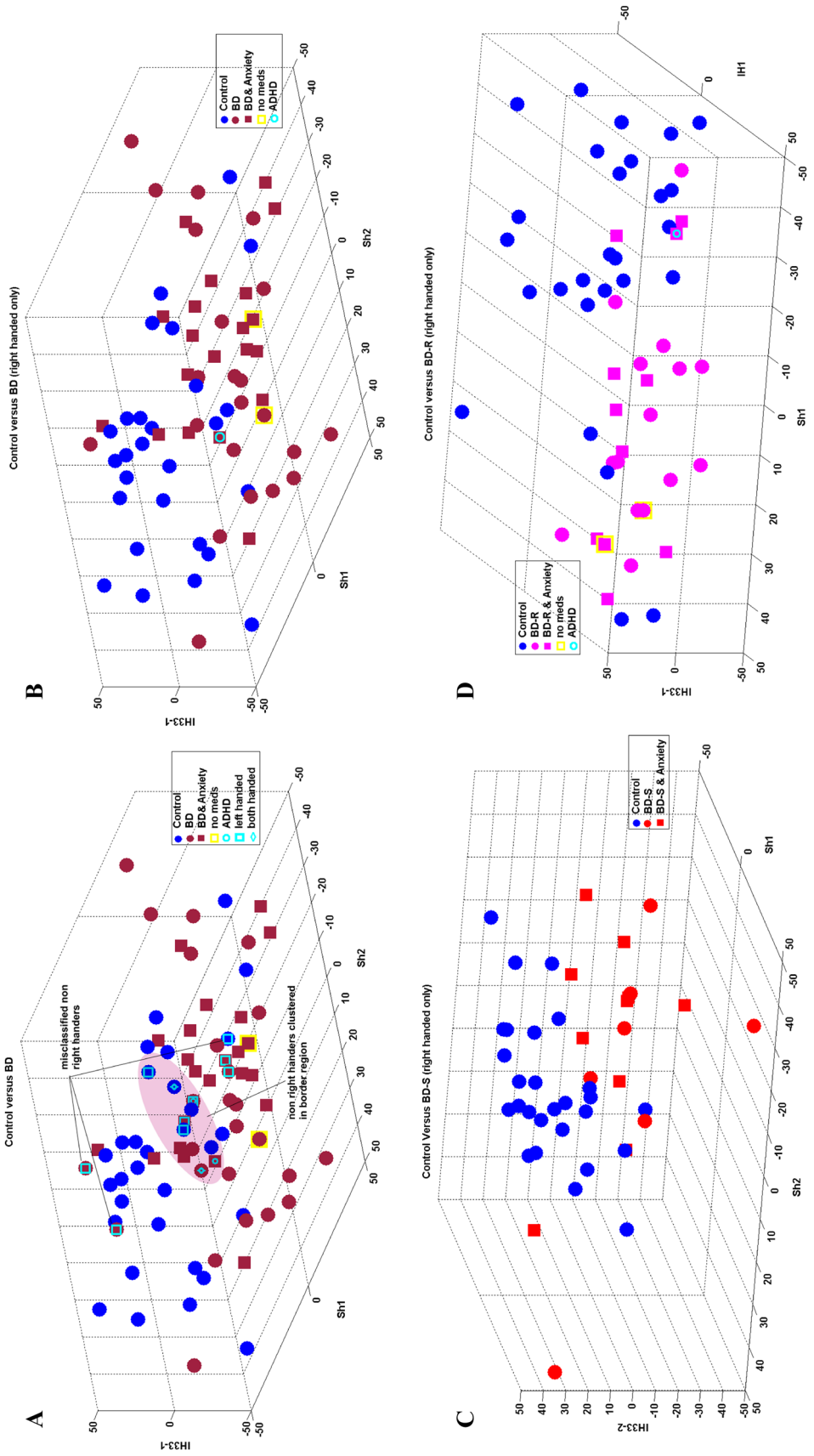

Fig. 5 Clustering of control and BD groups. **a** 3D plot of the clustering of control and BD groups for right, left and both handed participants using features Sh1, Sh2 and IH331. Left and both handed subjects are labelled and/or regionally shaded in pink. Note the shaded region is at the border between control and BD groups. **b** Same plot as **a** but for right handed participants only. Note improved cluster separation. **c** 3D plot of the clustering of control and BD-S groups for right handed participants using features Sh1, Sh2 and IH33-2. **d** 3D plot of the clustering of control and BD-R groups for right handed participants using features Sh1, IH1 and IH33-1

were significantly correlated (Supplement: Feature correlations, Table S2). This was not surprising as feature $IH_{33}2$ is derived from IH2 data and IH1 is a right-hand variant of the left-hand feature IH2.

Anxiety

When each average BD, BD-S and BD-R (type I and II or type II) population feature values were compared for anxiety and non-anxiety groupings, features IH1 (BD, BD-R), IH2 (BD-S) and IH332 (BD-S, BD-R) were found with non-overlapping SE ranges (Supplement: Anxiety effects, Table S3c). An analysis of type II BD subjects shows there were no major LDA classifier performance reductions ($\leq 4\%$) with anxiety (Supplement: Anxiety effects, Table S3a, b) for control ($n=31$) versus BD ($n=25$ no anxiety, 12 anxiety) and control versus BD-R ($n=19$, 8). There were, however, potentially larger reductions in classifier accuracy observed for the control versus BD-S ($n=6$, 4) and BD-S versus BD-R classifiers for groups with anxiety, but given those groups had small sample sizes, the observed reductions can only be considered suggestive of anxiety reducing the accuracy of classifiers incorporating firing pattern (IH or IH_{33}) features (particularly $IH_{33}2$).

Symptomatology

Using only two features (Sh2 and IH332) Fig. 6a shows good LDA classification of BD-S from BD-R participants. Most of the non-right handers are clustered in the diagram close to the upper BD-S BD-R classifier border. For comparison Fig. 6b shows a 3D plot for right handed participants demonstrating clear clustering of BD-S and BD-R groups (leave-one-out accuracy 82%). In Fig. 6c we have rotated Fig. 6b and coloured the asymptomatic BD-R subjects green to demonstrate a visual transition from moderate-severe to mild to asymptomatic. With increased sample size it would be interesting to determine if these symptomatology transitions persist and becomes significantly meaningful.

Medication effects on features

Each feature was examined for the influence of the drug types antipsychotics (AP), antidepressants (AD) or mood stabilizers (MS). As there were only two non-medicated (NM) BD subjects, we tested for medication effects by combining subjects based on whether they were (or were not) on each drug type; then, measured the effective shift from the non-medication mean locus to the medicated mean locus for each classification feature (Supplement: Medication effects).

For BD group comparisons with controls (Table S4) the indications are that AP, AD or MS medications have no significant effect on features Sh1, IH1 or IH331. Features Sh2 and IH332 showed a significantly reduced feature separation distance between BD and control loci as well as between BD-S and BD-R loci (Table S5) with MS and or AP medications.

Tables S4 and S5 data are indicative that the classification ability of all the features, as applied to BD, BD-S and BD-R separations from control as well as BD-S separation from BD-R can be considered as not being significantly enhanced by MS, AD, or AP medication. In all cases where there was a significant change in separation distance (e.g., MSmed group loci to MSnomed group loci) it was a reduced classifier separation distance with medication, i.e., there was no enhancement of classifier ability with medication.

Discussion

The results of our study confirm the hypothesis that between BD participants and healthy controls and notably between participants with different levels of depressive symptoms, the EVestG measured responses differ significantly (Figs. 2, 3, 4, 5; Table 2b).

Features

Five of the six extracted EVestG features showed a small but significant ($p<0.05$) correlation with MADRS (Table 2c). MADRS has the advantage of being able to measure a heterogeneity of symptoms whereas each EVestG feature is likely reflective of one or a group of symptoms or even one of the physiological bases for a symptom or group of symptoms. Being able to separate BD-S and BD-R is suggestive of each having different pathophysiological manifestation. Table 2a ROC data show Sh1 and IH331 features having more utility as trait and the IH features as symptomology features.

Despite the best individual features individually achieving classification accuracies of 70+% (e.g., static feature Sh1 for control versus BD) the use of trait like and symptomatology like feature combinations that combine features representative of both static/background (Sh1, IH1, IH2) and dynamic responses (Sh2, IH331, IH332) markedly increased the accuracy. Perhaps a later application of the symptomology sensitive features could be investigated to support best medication selection and/or measurement of its efficacy.

Feature physiology

There is evidence that at the vestibular afferent/efferent and or hair cell level possible genetic, neurochemical, receptor

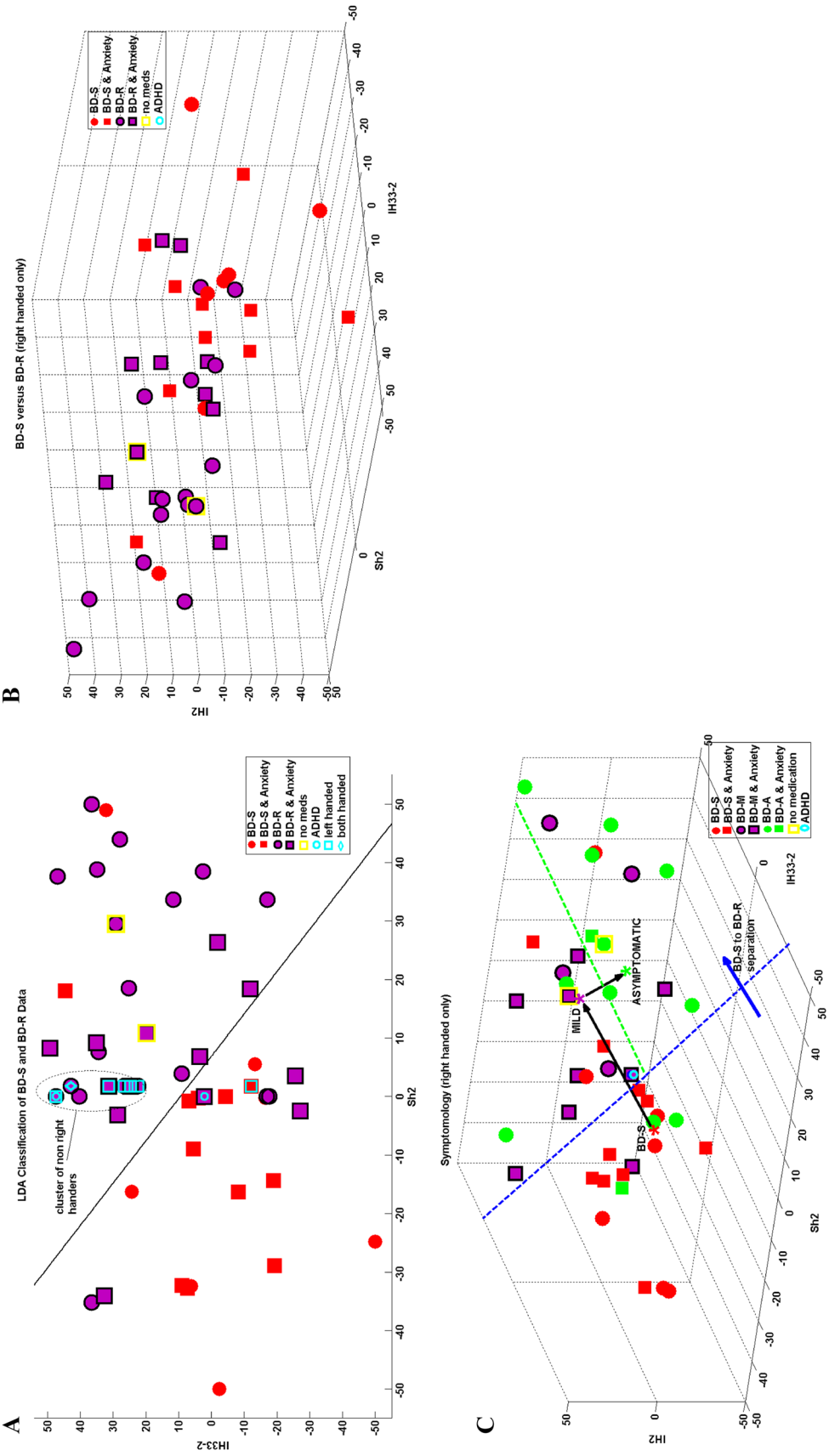

Fig. 6 Clustering of BD-S BD-R groups. **a** 2D two feature LDA classification of BD-S and BD-R populations using features Sh2 and IH332. The magenta colour used previously for BD-R is herein replaced by a dark purple with black edge to improve contrast with BD-R populations. Note the clustering of left or both handed subjects proximal to the classification surface. **b** 3D plot of the clustering of BD-S and BD-R groups for right handed participants using features Sh2, IH2 and IH332. **c** 3D plot of the clustering of BD-S and BD-R right handed subjects where within the BD-R group the BD-A (asymptomatic) participants have been plotted with green markers. The remaining BD-R group members are those with mild symptoms (BD-M). Asterisks are the mean loci for each BD group. Note this plot uses the same features as **b** and is a rotated version of **b** to better highlight the potential symptomatology transition from BD-S to mild to asymptomatic. The blue dotted line divides the plot into right and left sides and represents classification of BD-S and BD-R. On the right side (BD-R side) the green line is a visually applied arbitrary transition line between mild (upper right) and asymptomatic (lower right) groups to highlight BD-M and BD-A clustering

and or metabolic changes consequent to BD are possible if not likely.

Genes related to the axonal initial segment, calcium channels, circadian rhythm [30], and oligodendrocyte-myelin [31, 32] have been linked to BD.

Depression treatments that disrupt Ca^{2+} regulation or increase levels of monoamines, including serotonin, norepinephrine or dopamine, can all potentially trigger mania, implicating all these substances in its etiology [33]. Genetic or drug induced changes in channel kinetics have been shown to alter the acoustic compound action-potential [28] and by inference the Sh features used herein. Thus, Ca^{2+}, K^+ and Na^+ mechanism changes linked to repolarization and depolarization, as earlier mentioned, may assist in explaining the Sh feature differences observed in BD and control classifications. For example, pharmacological modification of the $Na_V1.7$ sodium channel can influence the excitability and discharge pattern of the vestibular afferent and VN neurons [34]. Similarly, with respect to the IH (and consequently IH33) features, physiological mechanisms that influence spontaneous activity and threshold may also provide some explanation.

In BD, cortically, there is evidence of α7 (nicotinic) and M2 (muscarinic) acetylcholine receptor binding change [35, 36]. These receptors are also located in the vestibular periphery [37–40], Vestibular Nucleus [34, 41] and Locus Coeruleus [42, 43]. Providing at least one mode by which the features used herein may be altered in BD, activation of the muscarinic acetylcholine receptor inhibits a low-threshold, voltage-gated K^+ current in a large proportion of vestibular afferent neurons; that, in turn, regulates neuronal excitability by tuning the membrane potential about the threshold level and participating in spike-frequency adaptation [44]. For example, the muscarinic drug scopolamine (a vestibular sedative often used to treat motion sickness) can produce antidepressant activity [45] by spike-frequency adaption [44]. Similarly, in BD following administration of nicotinic cholinergic receptor antagonists depressive symptoms decrease [38]. Nicotinic receptors also play an important role in regulating the activity of GABA neurons [46].

There appears to be a strong association between BD and polymorphisms at the level of $GABA_A$ receptor subunit genes [47]. GABA levels in plasma and CSF may be reduced in BD [47] reducing inhibition and potentially facilitating the spontaneous discharge of the vestibular afferents. However, there is evidence that GABA is an afferent neurotransmitter in the vestibular periphery and may be co-localized with glutamate. Cortes [48] suggests Glutamate preserves its co-transmitter role and GABA could act as a facilitator in the spontaneous discharge of the vestibular afferents by altering intracellular Ca^{2+} concentration. Reduced GABA as in BD may then lead to a de-facilitation in spontaneous discharge as observed herein for the IH features for BD-S compared to BD-R (Fig. 3). NDMA and AMPA receptors are also located in the VN [34]. BD is also linked to GluD1 receptor changes: GluD1 has a key role in glutamate metabolism and energy homeostasis [49]; it is highly expressed in the vestibular periphery [34, 50, 51], and expression changes may also lead to AMPA and NMDA synaptic abnormalities [49]. At the post-synaptic cell, glutamate interacts with AMPA/NMDA receptors which participate in determining the basal discharge and tonic response to sustained stimuli.

Limitations

1. Medication: The largest limitation of this study was that it was not possible to fully disentangle the impact of prescribed medication on the predominantly vestibular responses recorded. Critically, the number of non-medicated participants was small thus classification performance may have been influenced by medication. The feature combinations used in the control versus BD group and BD-S versus BD-R classifications achieved good separation (75–86%, Table 2b) despite showing significant decreases in classification separation distance for features Sh2 and IH332 with (MS and AP) and MS medications respectively (Tables S4, S5). These two features may in future studies prove useful in measuring the efficacy of MS medications. Importantly, there were no significant enhancements of classification with each medication type (Tables S4, S5). However, any conclusions remain constrained by the limitations of the medication analysis herein, the major limitations being:
    a. The pooling of medications into types MS, AD and AP. Within each type the mode of action, if fully described and known, can vary markedly between individual members of each type.
    b. The pooling of types into for e.g., MS (MS, MS&AP, MS&AD, MS&AD&AD) and non-MS (AP, AD, AP&AD, NM) meant pooling the effects of 1, 2 or 3 medication types together which may well mask or enhance individual (MS) effects.
2. Handedness: There are reported vestibular asymmetries depending on handedness [52]. The separation of BD groups from controls was sensitive to handedness for features Sh1 and $IH_{33}2$ (Table 2a). Removal of the non-right-handed subjects generally improved the classifier performance. However, for BD-S versus BD-R group classification removal of the non-right-handed subjects did not improve the classifier performance.
3. Anxiety: The features used in this study were not selected to highlight anxiety. However, the inclusion of subjects with anxiety may be a limitation as there is evidence for anxiety effecting the vestibular system

[10] and perhaps reducing the accuracy of the classifiers used herein (Table S3b). Herein, 3 of the 4 firing pattern features, in particular feature $IH_{33}2$, may, in a larger sample, be proven to be sensitive to anxiety. A current study is underway to study measure the effect of generalized anxiety disorder (GAD) on EVestG features deliberately selected to be sensitive to anxiety.

Clinical application

BD has a prevalence of around 4% [53], has a first time diagnostic accuracy of 31%, 60% of misdiagnosis is unipolar depression, and 35% wait > 10 years for correct diagnosis [54]. An EVestG can be recorded in under 1 h. An accuracy of around 80% was achieved for BD or MDD versus controls in this and a previous [4] study. In our recent study of major depressive disorder (MDD) [4] shape features were best applied toward MDD versus control classifications and interval features were best applied toward MDD symptomatology separations. Comparatively, combinations of shape and interval features delivered the best BD versus control as well as within BD symptomatology separations. This indicates BD and MDD may be separable using EVestG features. A study of this separation is currently ongoing.

Conclusions

Arguments for the potential impact of BD on the vestibular nucleus and vestibular periphery have been presented. We have provided evidence of the classification ability of EVestG derived features for separating BD, BD-S and BD-R from controls as well as for quantifying the symptomatology of BD-S from BD-R. Data are supportive of BD-S and BD-R having measurably different pathophysiological manifestations. Likely mechanisms affecting channel kinetics have been suggested. Future research should aim to determine the validity of these potential impacts with larger sample sizes and improved signal to noise ratio recordings. Additionally, future research should focus on studying a homogenous group of BD subjects who, if possible, are right handed as well as completely medication and anxiety free that then aims to compare activity in those participants and those in complete remission.

Acknowledgements We would like to thank all members of Monash Alfred Psychiatry Research Center who supported this research. Amber Garrett (a Ph.D. student) recorded many of the EVestG recordings. This work was supported by grants from the Australian Research Council and National Health and Medical Research Council. Neural Diagnostics Pty Ltd was the industry partner in this research. PF is supported by an NHMRC practitioner fellowship.

Author contributions BL wrote the first draft and did main data analysis; ZM and PF were the major contributors to the data analysis and paper writing; BL, PF, JK and CG conceived the experiment(s). PF and JK examined and referred the patients. CG and JM contributed to patient assessments. All authors reviewed the manuscript.

Funding Funding was provided by Australian Research Council (Grant no. LP0669420).

Compliance with ethical standards

Conflict of interest BL owns < 0.5% of shares in Neural Diagnostics Pty Ltd. (ND) and acts as a part-time consultant for ND. PF is supported by a NHMRC Practitioner Fellowship (1078567). PF has received equipment for research from MagVenture A/S, Medtronic Ltd, Cervel Neurotech and Brainsway Ltd and funding for research from Neuronetics and Cervel Neurotech. He is on the scientific advisory board for Bionomics Ltd. ZM, CG, JM, JK report no financial interests or potential conflicts of interest.

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