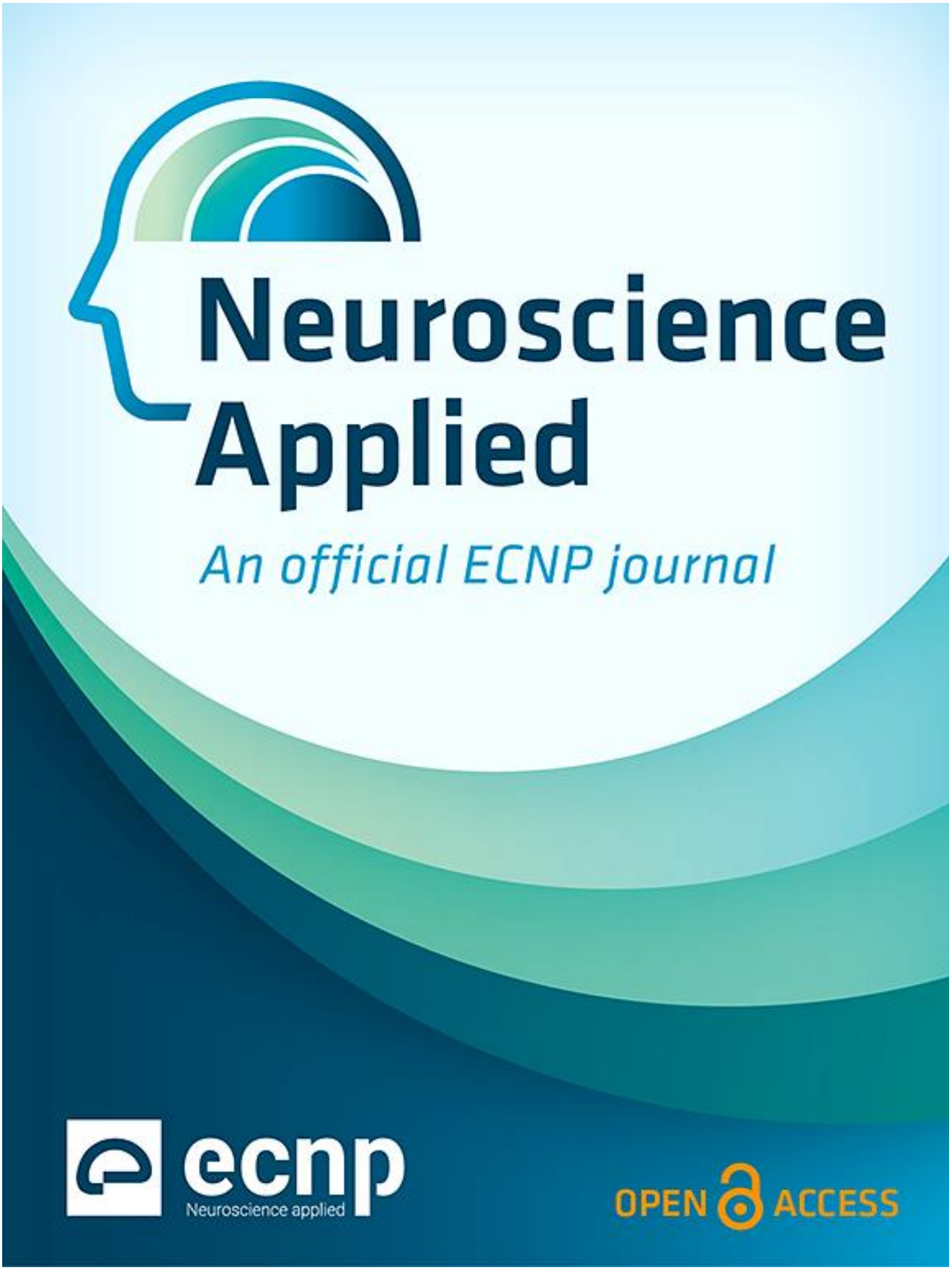
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within the therapeutic range (25-50ng/ml), no patient was underexposed, while the remaining 40 patients were underexposed. Median age body weight in the slow metabolizers group were 41 years [IQR: 27-47] and 77kg [IQR: 65-88,5], while in normal metabolizers group age and body weight were 35 years [IQR: 22-49] and 66kg [IQR: 59-88]. The drug level increase due to lower body weight and due to occurrence of CYP2C19*2 allele observed in the regression equation did not reach statistical significance.

Conclusion: While the result directionality was in accordance with the previously published studies, the effects of body weight and CYP2C19*2 allele occurrence were not significant in the analysed cohort. The absence of significant effects was likely due to still limited power of the study. Since this interim analysis includes only approximately one third of patients compared with what had been originally planned, it is expected that firmer conclusions related to the combined effect of CYP2C19 genotype and body weight on escitalopram exposure will emerge after all planned patients are included.

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No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2022.100763

P.0736

NEUROSCIENCE APPLIED 1 (2022) 100112 100764

Differential effects of repeated treatment with DOI and psilocybin on the head-twitch response (HTR), locomotor activity and anxiety-like behaviour

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Serotonin 5-HT2A receptors are widely distributed in the central nervous system and are thought to mediate the effects of psychedelic drugs. The 5-HT2A receptor has been identified as a potential therapeutic target for a number of psychiatric disorders, including anxiety and major depressive disorder (MDD). The aim of the present study was to investigate the effects of repeated administration of the psychedelic drugs DOI and psilocybin at two different treatment timepoints; 0h and 48h. For this purpose, we examined the head twitch response (HTR) which is widely used as a behavioural assay for 5-HT2A activation associated with rapid side-to-side rotational head movement. Locomotor activity and anxiety-like behaviour were also assessed in the open field.

Male C57BL/6J mice (n=56) were habituated to an open field arena (29cm x 36cm x 16cm) 30 minutes prior to testing. The mice received a single i.p. injection of either saline, DOI (0.5 mg/kg or 1 mg/kg), or psilocybin (0.3 mg/kg, 1 mg/kg, 3 mg/kg or 5 mg/kg). Immediately post-treatment the mice were placed back in the test cage for 30 minutes. To assess HTR, the mice were observed for 20 minutes (n=4 per group). Mice were recorded using AnyMaze software for 30 mins to assess the effects of DOI and psilocybin on locomotor activity (m) and time (s) spent exploring the centre of the arena (n=7-8 per group). The above protocol was repeated 48h later to assess the effects of repeated treatment with either DOI or psilocybin on HTR, locomotor activity and time spent exploring the centre. One-way ANOVA was used for statistical analysis and an alpha level of 0.05 was used as a criterion for statistical significance.

Administration of DOI and psilocybin at all doses resulted in a significant increase in the number of head twitches at both time points (0h and 48h). DOI (0.5 mg/kg) significantly increased locomotor activity after the first treatment ($p < 0.05$) but not at subsequent 48h treatment. Furthermore, the 5 mg/kg dose of psilocybin reduced mobility after the first treatment ($p < 0.05$) but not at subsequent 48h treatment. It was observed that after the first treatment psilocybin at 3 mg/kg ($p < 0.01$) and 5 mg/kg ($p < 0.0001$) resulted in a significant reduction in time spent exploring the centre of the arena. After the second treatment (48h) DOI 0.5 mg/kg ($p < 0.05$), 1 mg/kg ($p < 0.05$) and psilocybin 1 mg/kg ($p < 0.01$), 3 mg/kg ($p < 0.01$) and 5 mg/kg ($p < 0.0001$) resulted in a significant reduction in the time spent exploring the centre.

A significant increase in HTR was observed following treatment of DOI and psilocybin at the 0h and 48h time points, indicating that repeated exposure to the compounds at these doses did not decrease the 5HT2A receptor response. Conversely, there were differences in locomotor activity and anxiety-like behaviour between first and second exposure to DOI and psilocybin. Taken together, this data suggest that prior exposure to DOI and psilocybin influences behavioural changes induced by the subsequent administration, which may have implications for clinical use.

No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2022.100764

P.0737

NEUROSCIENCE APPLIED 1 (2022) 100112 100765

Effects of personalized dosing based on drug plasma level quantification on effectiveness and safety of escitalopram treatment

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Background: Considering the negative impact of anxiety and depression on society and lack of emergence of new antidepressants, it is of paramount importance to utilize the available treatment options in the best manner possible. Escitalopram is a commonly prescribed antidepressant that is predominantly metabolized by the polymorphic CYP2C19 liver enzyme and consequently, CYP2C19 genotype affects escitalopram metabolism. Previous report showed a strong association between CYP2C19 genotype and escitalopram exposure [1]; therefore, CYP2C19 genotype is a potentially clinically relevant feature in escitalopram treatment, since underdosed patients exhibit lower escitalopram treatment effectiveness [2] and since escitalopram adverse drug reactions (ADR) are dose dependent [3]. Objective of this prospective cohort clinical trial is to evaluate the impact of escitalopram dose adjustment based on escitalopram exposure on treatment efficacy and safety.

Methods: In this prospective cohort study patients suffering from depression were assessed for potential clinical benefits of a personalized dosing regimen for escitalopram, which is based on therapeutic drug monitoring of escitalopram plasma level. Treatment effectiveness was evaluated based on Hamilton depression rating scale (HAM-D), which was performed one day prior to escitalopram treatment initiation (Baseline, Visit 0), as well as after four (Visit 1) and eight (Visit 2) weeks of follow-up. Side effect assessment was based on Scandinavian UKU Side effects rating scale, which was performed at V1 and V2. In case of need, dose adjustment was performed at V1 and was guided by the measured steady state drug plasma level using HPLC two weeks after treatment initiation, with the aim to achieve the optimal exposure to escitalopram in every patient at V2. Relative change in HAM-D and UKU scale readouts from V1 to V2, were compared between comparator (dose was adjusted) and control (dose was not adjusted) groups by independent samples t-test and Chi-square test, respectively. The study protocol in full detail is available on clincaltrials.gov [4]

Results: To this day, 25 participants completed the study, and out of these, 19 participants required dose adjustment between visits. There were no statistically significant differences in the change in HAM-D scores from V1 to V2 between groups ($p>0.1$). In the comparator group, 11/19 patients reported ADRs, compared to 2/6 patients in control group. Appearance of new, or worsening of

the existing ADRs between V1 and V2 was reported in 6/19 patients in the comparator group and in 1/6 patients in the control group. There was no statistically significant difference between groups in ADR emergence or worsening ($p>0.1$)

Conclusion: The dose of escitalopram in 19 participants was augmented, but did not show statistically significant improvement in treatment effectiveness when compared to control group. There was no statistically significant increase in ADR frequencies in the dose augmentation group either, which is in concordance with the hypothesis that dose increase in underdosed patients does not lead to the increase of ADR frequency and severity. Noteworthy, since this report represents interim analysis on a sample which is approximately one fourth of the planned cohort, the conclusions are not yet unequivocal.

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No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2022.100765

P.0739

NEUROSCIENCE APPLIED 1 (2022) 100112 100766

Classification of bipolar disorder from multi-site regional-based cortical morphology features using support vector machine technique

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Introduction: Bipolar Disorder (BD) represents a severe, disabling and life-threating disorder whose early diagnosis and personalized treatments constitute one of the greatest challenges in the management of psychiatric illnesses [1]. In this context, Machine Learning (ML) identification of neural biomarkers is widely used to promptly classify BD and subsequently choose appropriate intervention strategies [2]. However, an optimal performance of ML's classifier relies on large, multi-site dataset. Thus, the application of harmonization technique as pre-processing stage appears necessary to remove site's effects heterogeneity, while preserving trends in the data created by biological variables. In this study, we adapted ComBat harmonization's pipeline of regional (ROI) volume- and surface-based measures in a multisite context to differentiate BD from control subjects (HC), investigating the critical features that contribute most for the classification at individual subject level.

Methods: ROI-based grey matter volume (GMV) and cortical thickness (CT) measures for the Desikan-Killiany atlas were obtained using the Freesurfer software from multi-site (n=5) T1-weighted MRI images of 245 BD subjects and 245 HC subjects, matched for age and sex, collected in the context of the StratiBip consortium. Sample numerosity balance between sites was maintained in BD and HC sets. First, GMV and CT ROI-based values across sites were harmonized using ComBat, while considering age, sex, and globally harmonized total intracranial volume contributions. As follow, PRONTO Support Vector Machine (SVM) was applied to classify BD from HC using harmonized ROI-based GMV and CT features, employing 5-fold nested cross validation (CV) and 10-fold CV for external loop. The most important ROI-based features for BD vs. HC classification were extracted.

Results: The SVM model differentiates classes with an accuracy of 63% for GMV features (65,37% for BD and 60,75% for HC) and 69% related to CT features (66,60% for BD and 71,78% for HC). The area under the receiver operating characteristic curve (ROC-AUC) was 67,71% and 76,97% respectively achieved for GMV and CT features. The regions that most contributed for BD vs HC classification from GMV data were Left Putamen, Right Lingual gyrus, Right Putamen, Right Lateral Occipital gyrus, Right Inferior Parietal cortex and Left Thalamus. For CT data, the regions that highly contribute to the classification model were Right Transverse Temporal cortex, Right Banks Superior Temporal sulcus, Right Precentral gyrus, Left Lingual, Right Precuneus cortex and Left Medial Orbitofrontal gyrus.

Conclusions: Our preliminary results provide a reasonable estimate of classification performance in a multi-site context preceded by an essential multi-center harmonization step, achieved using an adaptation of ComBat technique on ROI-based data. The SVM model allowed us to analyse the contribution of individual regions to the overall classification model for both ROI-based GMV and CT features, related to BD and HC sets. Our results support previous literature evidences, which show that significant regions of difference in BD and HC subjects include Precentral areas, Putamen [3], as well as Transverse Temporal gyrus [4], Thalamus and Parietal cortex [5].

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No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2022.100766

P.0740

NEUROSCIENCE APPLIED 1 (2022) 100112 100767

A multimodal automatic recognition and early treatment predictors in bipolar disorder

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Background: Bipolar disorder is a mental health disorder that causes mood swings that range from depression to mania. Automated processing in the diagnosis of bipolar disorder can help providing quantitative indicators, and allow easier observations of the patients for longer periods.

Objectives To create a multimodal decision system for three level mania