Evaluation of the wireless dry EEG Cumulus platform to conduct neurocognitive research

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Cumulus™

Florentine Marie Barbey, MSc

Thesis submitted for the degree of

Doctor in Philosophy

in the School of Psychology at Trinity College Dublin,

Ireland

2022

Academic Supervisor

Dr Robert Whelan

Industrial Supervisor

Dr Brian Murphy

I Declaration

I, Florentine Marie Barbey, declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

I do not consent to the examiner retaining a copy of the thesis beyond the examining period, should they so wish (EU GDPR May 2018).

Signed,

Florentine Barbey

31st December 2022

II Disclosure, funding, and conflict-of-interest

This thesis was funded by the Employment-Based Postgraduate Programme of the Irish Research Council. This program has been designed to promote collaborations between industries and higher education institutions. In this program, the postgraduate researcher is based in and employed by their employment partner. I, Florentine Marie Barbey, have been a full-time employee at Cumulus Neuroscience Ltd, the industry that developed the electroencephalography technology evaluated in this thesis. I participated in the design and development of the Cumulus technology before and during my PhD program, and received funding from Cumulus throughout the completion of my PhD program.

The analyses presented in this thesis are commercially sensitive and contain proprietary information. There will be a strict embargo on this thesis and some of the proprietary aspects of the technology will not be described. The host industry and technology provider Cumulus Neuroscience Ltd provided the key information on the tasks and analyses necessary for the interpretation of the results. However, it may be in certain cases that less information is provided to the reader than is usual in the field (e.g., to prevent the replication of the proprietary aspects of the technology). These are discussed in the General Discussion chapter of this thesis and described in the limitation of this research.

III Summary

The identification and validation of reliable brain biomarkers to characterize neuropsychiatric and neurodegenerative disorders can be laborious and generally relies on time-consuming brain imaging methods. Brain activity is typically assessed using costly and non-portable MRI or PET scan technology which do not lend themselves to repeated use. Electroencephalography (EEG) consists of recording voltage fluctuations at the surface of the scalp and are informative of brain functions and cognition. A growing number of portable EEG devices are now being developed to enable the repeated sampling of brain activity remotely (i.e., outside of the laboratory) by participants themselves. These cutting-edge technologies make use of new types of electrodes that can be effortlessly placed onto the scalp without any kind of preparation or need for conductive gel. The possibility of conducting repeated EEG studies outside of the laboratory hold many promises regarding the identification of new disease biomarkers. It is expected that repeated measurements will allow the isolation of metrics more robust to lifestyle factors and fluctuating disease symptoms. Before deploying these new systems in clinical populations, it is necessary to study the feasibility and validity of the proposed method. The objective of this thesis was to characterise and explore this new way of collecting brain data by looking at the deployment of a neurocognitive platform indicative of this kind of approach outside the laboratory. Specifically, my analyses were centred around the Cumulus Neuroscience platform (www.cumulusneuro.com). This platform includes a wireless dry EEG headset coupled with an Android tablet for cognitive task presentation. At the beginning of a study, participants are invited to the laboratory to get familiarised with the technology and are then invited to take the hardware home to record sessions autonomously.

Empirical Chapter 1 was aimed at evaluating the usability and validity of the approach by conducting post-hoc analyses of two at-home datasets collected in the context of other research.

The first dataset included 50 older adults (>55-years-old) and the second 30 young male adults (mean age=25.6 years-old). I quantified the usability of the platform by looking at adherence to the study protocol, participants' subjective feedback and percentage of successful sessions. Further, data quality was evaluated using an established metric of quality within the field and results were compared to a representative study using the traditional gold-standard technology. I found that on average, adherence was very high across the two groups and usability analyses did not reveal any differences between the younger and older cohorts. However, data collected in the older group was substantially noisier compared to the younger dataset and many more trials were discarded during signal preprocessing. When comparing my results to the gold standard, I found that between 2 to 3 at-home sessions needed to be aggregated to reach similar noise levels when comparing similar cohorts.

Empirical Chapter 2 was a use-case study of the platform when deployed within the context of a pharmacological study. My test case was a ketamine challenge study during which thirty young healthy males received in a double-blind cross-over design two infusions of ketamine and of saline solutions four weeks apart. The protocol included intensive bursts of data collection in the laboratory immediately before and after the infusions under research supervision to capture acute drug effects. Additionally, data was collected remotely from the home a week before and after each intervention to measure any persistent drug effect. The primary objective of this study was to evaluate if the neurocognitive dry EEG platform studied here could emulate results from the wet EEG literature. The second objective of this study was exploratory and evaluated if at-home unsupervised self-administered dry EEG could capture any persistent drug effects. I targeted the best-characterised EEG endpoints studied within the context of ketamine: resting state power spectrum modulations as well as the mismatch negativity event-related potential (ERP). Furthermore, I also targeted electrophysiological markers that have been associated with the anterior cingulate and prefrontal cortices activities (i.e., the Event-Related Negativity – ERN, and the P300). The data collected with the dry EEG platform only partially emulated the wet EEG

literature. Although, I observed the well-described gamma enhancement during the ketamine infusion, no other analyses yielded significant results. Other important factors unrelated to the technology itself, such as the timing of the sessions and the drug dosage may have contributed to the lack of significant results. Data collected in the home suggested that there was no persistent effect of ketamine on electrophysiological markers of cognitive functions in the week after the infusions.

Empirical Chapter 3 consisted in of an in-depth evaluation of a gamified Oddball task and its suitability to elicit a widely used and well characterized ERP in the EEG field: the P300. Gamified cognitive tasks are becoming popular within psychology research. However, very few studies have looked at their validity with respect to the elicitation of ERPs. In this chapter, I explored the effect of task gamification and repeated task administration on the elicitation the P300. I recruited 10 young adults from the local community and asked them to complete a gamified 2-stimulus Oddball task multiple times both in the laboratory and the home. As I focused on gamification in isolation from the rest of the platform, EEG data were collected using a standard wet EEG system under researcher supervision in a controlled laboratory environment. Participants completed six consecutive EEG sessions in the laboratory, were sent home to complete 7 behaviour-only sessions on separate days and came back in the laboratory to complete 6 consecutive additional EEG sessions. I evaluated ERP morphologies, timings, and topographies. I also looked the stability of the signals over time and asked participants for qualitative feedback on their strategies. Participants' questionnaires revealed that individuals' strategies were quite heterogenous and that sometimes participants could change strategy over time. I observed well-defined ERPs, with consistent morphologies and timings across all participants in accordance with what is reported in the literature. Topographical results were more mixed. The target P300 yielded a topography consistent with the literature whereas the Non-Target P300s were more anterior than expected. These results suggest that gamification features impacted the nature of cognitive functions at play during the task.

Overall, this thesis evaluated key features of remote dry EEG, showing that it is easily deployable in participants' home environment. Participants found the platform quite usable and repeatedly engaged with it while in the home. Data quality matched that observed in wet EEG. The use-case pharmacological trial demonstrated that it is possible to successfully deploy the technology in the context of a drug study that included intensive burst of recordings occurring alternatively in the home or the laboratory. My results only partially emulated the wet EEG literature, but it is likely that other factors unrelated to the technology itself prevented a complete emulation. The in-depth gamification analyses revealed that a gamified EEG task could elicit consistent ERPs within participants, although across participants different strategies could have resulted in the generation of different types of P300. To summarise, I have shown that remote, self-administered, gamified EEG is a valid approach for the study of neurocognition.

IV List of Publications and Presentations

Publications

This thesis incorporates material already published in the manuscript listed below:

Empirical Chapter 1:

Barbey FM, Farina FR, Buick AR, et al. Neuroscience from the comfort of your home: Repeated, self-administered wireless dry EEG measures brain function with high fidelity. *Front Digit Heal*. 2022;4(944753). doi:10.3389/fdgth.2022.944753

Part of the introduction and general discussion:

Whelan R, **Barbey FM,** Cominetti MR, et al. Developments in scalable strategies for detecting early markers of cognitive decline. Transl Psychiatry 12, 473 (2022). https://doi.org/10.1038/s41398-022-02237-w

Manuscript in preparation:

Barbey F, Bianchi M, et al. Demonstration of a novel wireless EEG platform to detect the acute and long-term effects of ketamine, in the lab and in the home.

Conference posters

Murphy B, **Barbey F,** Bianchi M, et al. Demonstration of a novel wireless EEG platform to detect the acute and long-term effects of ketamine, in the lab and in the home. In: *FENS, Glasgow*; 2020.

Rueda-Delgado, L. M., Nolan, H., Buick, A. R., **Barbey, F**., Dyer, J., McGuinness, B., ... & Murphy, B..

Evaluation of adaption skills in older adults using behavioural and EEG repeated measurements during a visual oddball object detection task: Biomarkers (non-neuroimaging)/Longitudinal change over time. In: *Alzheimer's & Dementia*, 16, e042575, *Online*; 2020

Barbey F, Farina FR, Buick AR, et al. Longitudinal, self-administered, wireless dry EEG reliably measures neurophysiological basis of cognitive processes in older adults. *15th Int Conf Alzheimer's Park Dis*. *Online*; 2021. doi:10.13140/RG.2.2.16354.66249

Barbey FM, Farina FR, Buick AR, Rueda-Delgado LM, Dyer JF, Islam, M.N., Murphy B, Nolan H, and Whelan R. Neurocognitive testing from the home: Statistical power of repeated, self-administered wireless dry EEG. *Organisation for Human Brain Mapping (OHBM), Glasgow*; 2022.

Buick A, Murphy B, Dyer J, **Barbey F,** Nolan H, McWilliams E, Real-world functional neurophysiology: unsupervised task-driven EEG for home-based clinical research. *Organisation for Human Brain Mapping (OHBM), Glasgow*; 2022.

Barbey F, Buick A, Danyeli L, et al. Repeat at-home sampling of gamified behavioural tasks and wearable dry-EEG can match the quality of lab- based systems. In: *Federation of European Neuroscience Societies*, *Paris*; 2022.

Rueda-Delgado, L.M., **Barbey, F.M.,** Buick, A.R., Dyer, J.F., Farina, F., Islam, M.N., McGuinness, B., Nolan, H., Passmore, A.P., Whelan, R., Murphy, B.. Cognitive performance in older adults using home-based EEG repeated measurements. In: *IEEE Engineering in Medicine and Biology Conference (EMBC), Glasgow*; 2022.

Islam, M.N., **Barbey F.,** Buick A., Nolan H., Rueda-Delgado L.M., Murphy B. Feasibility and reliability of real-world functional neurophysiology with at-home use of Cumulus' wireless EEG. In: *International Pharmaco-EEG Society (IPEG), New York City;* 2022.

V Acknowledgements

The completion of this doctoral thesis has been an enormous endeavour that could not have happened without the help of several key individuals. First, I would like to thank my supervisors Prof. Rob Whelan and Dr. Brian Murphy for agreeing to work together and bridge the industry and academic world so that I could complete the PhD project of my dream. I cannot thank you enough for your patient, diligent, and inspiring supervision which has led to the completion of this project. Working alongside you and following your examples allowed me to learn a lot and improve numerous key skills by watching your incredible scientific rigorousness, attention to details, and unshakable poise in front of very fast approaching deadlines and head-wrecking problems. I am also in debt to Dr. Francesca Farina who made the first empirical chapter of this thesis possible by kindly sharing with me one of the datasets collected within the context of her post-doctoral studies. Similarly, I wish to extend my thanks to the whole team of the CANLAB laboratory of the university of Magdeburg, Germany, who participated in the dataset collection of the second empirical chapter. Finally, the third empirical chapter of this thesis would not have existed without the invaluable help of Tom Farnan and Alannah Smith who assisted with the wet EEG data collection.

I would also like to address a massive thank you to the Cumulus Neuroscience team for their unwavering technical and emotional support during the completion of this project. A special thank you to the Science team: John Dyer, Alison Buick, Esther McWilliams, Hugh Nolan, Raju, and Laura Rueda-Delgado for making each day working together a pleasure and for your numerous and invaluable inputs on my work. Even if most of this PhD happened virtually while working from home during the Covid-19 pandemic, I never felt disconnected or isolated thanks to you.

Finally, I would also like to acknowledge the invaluable support and motivation my friends and family provided throughout this journey. A special thank you to Ines, Emma, Marie-Estelle, Mum,

Sara, Conor and all the others that I cannot name here. Our hikes, parties, meals, and many other activities have allowed me to keep going and protected my sanity during these years.

Florentine Barbey

This research was supported by the Irish Research Council, Cumulus Neuroscience Ltd., and Trinity College Dublin.

VI List of Tables

Table 1: Technical specifications of the Cumulus dry EEG recording headset. 63

Table 2: ERPs of interest from the ERP CORE reference wet EEG dataset 80

Table 3: Participant demographics. 81

Table 4: Statistical Analyses of the System Usability Scale. 84

Table 5: Linear mixed effect model estimates and Wald tests of behavioural data. 87

Table 6: Mean number of available trials after processing and percentage of data discarded per session per participant. 89

Table 7: Number of available at-home sessions at each step of the data collection analysis, including percentage retained relative to previous step. 90

Table 8: Count of usable sessions per channel. 92

Table 9: Hypothesised effects as suggested by the literature. 119

Table 10: Investigational and control compounds used. 120

Table 11: List of the questionnaires administered in the study. 123

Table 12: Electrode sites, time-locking event and baseline period for each component. 125

Table 13: Summary table of the demographics of the participants 128

Table 14: Summary table of the EEG recordings collected during the research study. 129

Table 15: Plasma concentration of ketamine, norketamine and hydroxy-norketamine 20 mins and 40 mins after the beginning of the infusion. 135

Table 16: Linear mixed effect model estimates and Wald tests of the Reaction time during the gamified visual Oddball. 140

Table 17: Linear mixed effect model estimates and Wald tests of the Reaction time during the gamified Flanker task to all successful trials. 143

Table 18: Linear mixed effect model estimates and Wald tests of difference of reaction time between incongruent minus congruent trials in the Gamified Flanker Task. 146

Table 19: Summary table of all behavioural metrics broken down per day across all subjects. 148

Table 20: Questionnaire data from Subject 1. 180

Table 21: Questionnaire data from Subject 2. 189

Table 22: Questionnaire data from Subject 3. 199

Table 23: Questionnaire data from Subject 4. 209

Table 24: Questionnaire data from Subject 5. 219

Table 25: Questionnaire data from Subject 6. 229

Table 26: Questionnaire data from Subject 7. 248

Table 27: Questionnaire data from Subject 8. 258

Table 28: Questionnaire data from Subject 9. 267

VII List of Figures

Figure 1: **Schematic representation of fluctuation in cognitive functioning across time.**.....32

Figure 2: Canonical P300 ERPs from the ERP Core open-source dataset.. 40

Figure 3: Canonical MMN ERPs from the ERP Core open-source dataset......41

Figure 4: Canonical ERN ERPs from the ERP Core open-source dataset......43

Figure 5: Electroencephalography recording set-up......46

Figure 6: Diagram of the younger adult study design.....59

Figure 7: Infusion Day protocol.....60

Figure 8: Cumulus dry EEG recording headset. 64

Figure 9: Cumulus dry EEG recording headset scheme......64

Figure 10: Screenshots of the gamified Oddball task.. 67

Figure 11: Screenshots of Gamified Adaptive Flanker task. 68

Figure 12: Screenshots of Gamified Mismatch Negativity task......69

Figure 13: Weekly at-home adherence to the experimental protocol......83

Figure 14: Median System Usability Scale component scores.....83

Figure 15: Behavioural responses to the gamified tasks during the first seven sessions.....86

Figure 16: Percentage of available sessions after pre-processing per channel. 91

Figure 17: Mean percentage of trials rejected across time. 93

Figure 18: ERPs analyses extracted from the Younger Adult Study (N=30). 96

Figure 19: Standardized Measurement Errors per number of trials of data collected in the laboratory under researcher supervision extracted from the Younger Adult Study (N=30)......97

Figure 20: Topographic maps of the event-related potentials collected during the Younger Adult Study. 98

Figure 21: Event-related potentials collected during the Younger Adult Study extracted from the Oddball task locked to the Target stimulus presentation. 99

Figure 22: Event-related potentials collected during the Younger Adult Study extracted from the Flanker task locked to participants' response to the Correct Trials. 100

Figure 23: Event-related potentials collected during the Younger Adult Study extracted from the Flanker task locked to participants' response to the Correct Trials. 101

Figure 24: ERPs analyses extracted from the Older Adult Study (N=50). 104

Figure 25: Standardized Measurement Errors per number of trials of data collected in the laboratory under researcher supervision extracted from the Older Adult Study (N=50). 105

Figure 26: Topographic maps of the event-related potentials collected during the Younger Adult Study. 106

Figure 27: Event-related potentials collected during the Older Adult Study extracted from the Oddball task locked to the Target stimulus presentation. 107

Figure 28: Event-related potentials collected during the Older Adult Study extracted from the Flanker task locked to participants' response to the Correct Trials. 108

Figure 29: Event-related potentials collected during the Older Adult Study extracted from the Flanker task locked to participants' response to the Error Trials. 109

Figure 30: Precision in time spacing between infusion and post-infusion sessions (EEG and blood draws). 130

Figure 31: CADSS scores before, an hour after and 24h hrs after the ketamine and saline infusions. 132

Figure 32: MADRS scores before, an hour after and 24h hrs after the ketamine and saline infusions. 133

Figure 33: Item-wise MADRS scores one hour after ketamine infusion. 134

Figure 34: Boxplot of the evolution of the plasma concentration of ketamine and its metabolites 20 and 40 mins after the beginning of the infusion. 136

Figure 35: Paired plot comparisons of plasma concentrations of ketamine and its metabolites 20 and 40 mins after the beginning of the infusion. 137

Figure 36: Distribution of the plasma concentration of ketamine and its metabolites 20 and 40 mins after the beginning of the infusion. 138

Figure 37: Reaction time to Target trials in the gamified Oddball across days after the ketamine infusion 141

Figure 38: Reaction time to Target trials in the gamified Oddball across days after the saline infusion 141

Figure 39: Reaction time to Correct trials in the gamified Flanker across days after the ketamine infusion 144

Figure 40: Reaction time to Correct trials in the gamified Flanker across days after the saline infusion 144

Figure 41: Difference of reaction time between incongruent minus congruent trials in the Gamified Flanker Task across days after the ketamine infusion. 147

Figure 42: Difference of reaction time between incongruent minus congruent trials in the Gamified Flanker Task across days after the saline infusion. 147

Figure 43: Resting State Power Spectral Density during the second half of the infusion. 149

Figure 44: T-values extracted from the one-sided paired t-test statistical analyses of the power spectral density during the second half of the infusion. 150

Figure 45: Resting State Power Spectral Density collected in the laboratory before, 1 hr after and 24 hrs after the infusions. 151

Figure 46: Resting State Power Spectral Density collected in the home during the week before, day 2 to 4 days after, and 5 to 7 days after the infusions. 152

Figure 47: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the laboratory. 153

Figure 48: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the home. 154

Figure 49: Mismatch Negativity Task before, during, 1h after, and 24h after each infusion. ... 155

Figure 50: Mismatch Negativity Task during the week after the ketamine and saline infusions. 156

Figure 51: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the laboratory. 157

Figure 52: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the home. 158

Figure 53: Grand average ERPs extracted from Astrotap locked to Target stimulus. 160

Figure 54: Grand average ERPs extracted from Astrotap locked to Target stimulus. 161

Figure 55: F-values extracted from the repeated Two-way ANOVAs conducted on Astrotap data collected in the laboratory. 162

Figure 56: F-values extracted from the repeated Two-way ANOVAs conducted on astrotap data collected from the home. 163

Figure 57: Grand average ERPs extracted from Go With The Flow locked to participants' responses. 165

Figure 58: Grand average ERPs extracted from Go With The Flow locked to participants' responses. 166

Figure 59: F-values extracted from the repeated Two-way ANOVAs on Go With The Flow data collected in the laboratory.. 167

Figure 60: F-values extracted from the repeated Two-way ANOVAs on Go With The Flow data collected in the home. 168

Figure 61: Diagram of the study design. 175

Figure 62: Behavioural responses of Subject 1. 181

Figure 63: Mean event-related potentials for each session extracted around clusters of interest for Subject 1. 182

Figure 64: Event related potentials traces around clusters of electrodes of interest for Subject 1 during the first visit in the laboratory. 183

Figure 65: Event related potentials traces around clusters of electrodes of interest for Subject 1 during the last visit in the laboratory. 184

Figure 66: Topographic maps of event related potentials of Subject 1 to Target trials during the first visit in the laboratory. 185

Figure 67: Topographic maps of event related potentials of Subject 1 to Target trials during the last visit in the laboratory. 186

Figure 68: Topographic maps of event related potentials of Subject 1 to Non-Target trials during the first visit in the laboratory. 187

Figure 69: Topographic maps of event related potentials of Subject 1 to Non-Target trials during the last visit in the laboratory. 188

Figure 70: Behavioural responses of Subject 2. 190

Figure 71: Mean event-related potentials for each session extracted around clusters of interest for Subject 2. 192

Figure 72: Event Related potentials traces around clusters of electrodes of interest for Subject 2 during the first visit in the laboratory. 193

Figure 73: Event Related potentials traces around clusters of electrodes of interest for Subject 2 during the last visit in the laboratory. 194

Figure 74: Topographic maps of event related potentials of Subject 2 to Target trials during the first visit in the laboratory. 195

Figure 75: Topographic maps of event related potentials of Subject 2 to Target trials during the last visit in the laboratory. 196

Figure 76: Topographic maps of event related potentials of Subject 2 to Non-Target trials during the first visit in the laboratory. 197

Figure 77: Topographic maps of event related potentials of Subject 2 to Non-Target trials during the last visit in the laboratory. 198

Figure 78: Behavioural responses of Subject 3. 200

Figure 79: Mean event-related potentials for each session extracted around clusters of interest for Subject 3. 202

Figure 80: Event Related potentials traces around clusters of electrodes of interest for Subject 3 during the first visit in the laboratory. 203

Figure 81: Event Related potentials traces around clusters of electrodes of interest for Subject 3 during the last visit in the laboratory. 204

Figure 82: Topographic maps of event related potentials of Subject 3 to Target trials during the first visit in the laboratory. 205

Figure 83: Topographic maps of event related potentials of Subject 3 to Target trials during the last visit in the laboratory. 206

Figure 84: Topographic maps of event related potentials of Subject 3 to Non-Target trials during the first visit in the laboratory. 207

Figure 85: Topographic maps of event related potentials of Subject 3 to Non-Target trials during the last visit in the laboratory. 208

Figure 86: Behavioural responses of Subject 4. 210

Figure 87: Mean event-related potentials for each session extracted around clusters of interest for Subject 4. 212

Figure 88: Event Related potentials traces around clusters of electrodes of interest for Subject 4 during the first visit in the laboratory. 213

Figure 89: Event Related potentials traces around clusters of electrodes of interest for Subject 4 during the last visit in the laboratory. 214

Figure 90: Topographic maps of event related potentials of Subject 4 to Target trials during the first visit in the laboratory. 215

Figure 91: Topographic maps of event related potentials of Subject 4 to Target trials during the last visit in the laboratory. 216

Figure 92: Topographic maps of event related potentials of Subject 4 to Non-Target trials during the first visit in the laboratory. 217

Figure 93: Topographic maps of event related potentials of Subject 4 to Non-Target trials during the last visit in the laboratory. 218

Figure 94: Behavioural responses of Subject 5. 220

Figure 95: Mean event-related potentials for each session extracted around clusters of interest for Subject 5. 222

Figure 96: Event Related potentials traces around clusters of electrodes of interest for Subject 5 during the first visit in the laboratory. 223

Figure 97: Event Related potentials traces around clusters of electrodes of interest for Subject 5 during the last visit in the laboratory. 224

Figure 98: Topographic maps of event related potentials of Subject 5 to Target trials during the first visit in the laboratory. 225

Figure 99: Topographic maps of event related potentials of Subject 5 to Target trials during the last visit in the laboratory. 226

Figure 100: Topographic maps of event related potentials of Subject 5 to Non-Target trials during the first visit in the laboratory. 227

Figure 101: Topographic maps of event related potentials of Subject 5 to Non-Target trials during the last visit in the laboratory. 228

Figure 102: Behavioural responses of Subject 6. 230

Figure 103: Mean event-related potentials for each session extracted around clusters of interest for Subject 6. 232

Figure 104: Event Related potentials traces around clusters of electrodes of interest for Subject 6 during the first visit in the laboratory. 233

Figure 105: Event Related potentials traces around clusters of electrodes of interest for Subject 6 during the last visit in the laboratory. 234

Figure 106: Topographic maps of event related potentials of Subject 6 to Target trials during the first visit in the laboratory. 235

Figure 107: Topographic maps of event related potentials of Subject 6 to Target trials during the last visit in the laboratory. 236

Figure 108: Topographic maps of event related potentials of Subject 6 to Non-Target trials during the first visit in the laboratory. 237

Figure 109: Topographic maps of event related potentials of Subject 6 to Non-Target trials during the last visit in the laboratory. 238

Figure 110: Behavioural responses of all subjects. 239

Figure 111: Mean event-related potentials for each session extracted around clusters of interest for all subjects. 241

Figure 112: Event Related potentials traces around clusters of electrodes of interest for all subjects during the first visit in the laboratory. 242

Figure 113: Event Related potentials traces around clusters of electrodes of interest for all subjects during the last visit in the laboratory. 243

Figure 114: Topographic maps of event related potentials of all subjects to Target trials during the first visit in the laboratory. 244

Figure 115: Topographic maps of event related potentials of all subjects to Target trials during the last visit in the laboratory. 245

Figure 116: Topographic maps of event related potentials of all subjects to Non-Target trials during the first visit in the laboratory. 246

Figure 117: Topographic maps of event related potentials of all subjects to Non-Target trials during the last visit in the laboratory. 247

Figure 118: Behavioural responses of Subject 7. 249

Figure 119: Mean event-related potentials for each session extracted around clusters of interest for Subject 7. 251

Figure 120: Event Related potentials traces around clusters of electrodes of interest for Subject 7 during the first visit in the laboratory. 252

Figure 121: Event Related potentials traces around clusters of electrodes of interest for Subject 7 during the last visit in the laboratory. 253

Figure 122: Topographic maps of event related potentials of Subject 7 to Target trials during the first visit in the laboratory. 254

Figure 123: Topographic maps of event related potentials of Subject 7 to Target trials during the last visit in the laboratory. 255

Figure 124: Topographic maps of event related potentials of Subject 7 to Non-Target trials during the first visit in the laboratory. 256

Figure 125: Topographic maps of event related potentials of Subject 7 to Non-Target trials during the last visit in the laboratory. 257

Figure 126: Behavioural responses of Subject 8. 259

Figure 127: Mean event-related potentials for each session extracted around clusters of interest for Subject 8. 260

Figure 128: Event Related potentials traces around clusters of electrodes of interest for Subject 8 during the first visit in the laboratory. 261

Figure 129: Event Related potentials traces around clusters of electrodes of interest for Subject 8 during the last visit in the laboratory. 262

Figure 130: Topographic maps of event related potentials of Subject 8 to Target trials during the first visit in the laboratory. 263

Figure 131: Topographic maps of event related potentials of Subject 8 to Target trials during the last visit in the laboratory. 264

Figure 132: Topographic maps of event related potentials of Subject 8 to Non-Target trials during the first visit in the laboratory. 265

Figure 133: Topographic maps of event related potentials of Subject 8 to Non-Target trials during the last visit in the laboratory. 266

Figure 134: Behavioural responses of Subject 9. 268

Figure 135: Mean event-related potentials for each session extracted around clusters of interest for Subject 9. 269

Figure 136: Event Related potentials traces around clusters of electrodes of interest for Subject 9 during the first visit in the laboratory. 270

Figure 137: Event Related potentials traces around clusters of electrodes of interest for Subject 9 during the last visit in the laboratory.. 271

Figure 138: Topographic maps of event related potentials of Subject 9 to Target trials during the first visit in the laboratory. 272

Figure 139: Topographic maps of event related potentials of Subject 9 to Target trials during the last visit in the laboratory. 273

Figure 140: Topographic maps of event related potentials of Subject 9 to Non-Target trials during the first visit in the laboratory. 274

Figure 141: Topographic maps of event related potentials of Subject 9 to Non-Target trials during the last visit in the laboratory. 275

Figure 142: Behavioural responses of Subject 10. 276

Figure 143: Mean event-related potentials for each session extracted around clusters of interest for Subject 10. 278

Figure 144: Event Related potentials traces around clusters of electrodes of interest for Subject 10 during the first visit in the laboratory. 279

Figure 145: Event Related potentials traces around clusters of electrodes of interest for Subject 10 during the last visit in the laboratory.. 280

Figure 146: Topographic maps of event related potentials of Subject 10 to Target trials during the first visit in the laboratory. 281

Figure 147: Topographic maps of event related potentials of Subject 10 to Target trials during the last visit in the laboratory......282

Figure 148: Topographic maps of event related potentials of Subject 10 to Non-Target trials during the first visit in the laboratory. 283

Figure 149: Topographic maps of event related potentials of Subject 10 to Non-Target trials during the last visit in the laboratory. 284

VIII List of Abbreviations

Abbreviation/Term	**Definition**
ACC	Anterior Cingulate Cortex
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AIBL study	Australian Imaging, Biomarkers and Lifestyle study
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMT	Amazon Mechanical Turk
Astrotap	Gamified oddball task, developed by Cumulus
BCI	Brain-Computer Interface
BD	Bipolar Disorder
BDNF	Brain Derived Neurotrophic Factor
CADSS	Clinician-Administered Dissociative States Scale
CR	Coefficients of Repeatability
CU	Cognitively Unimpaired
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiography
EEG	Electroencephalography
EOG	Electro-oculogram
ERN	Error-Related Negativity
ERP	Event-Related Potential
FDA	Federal Drug Agency
GABA	Gamma-Aminobutyric Acid

GWTF	Go With The Flow, Gamified flanker task developed by Cumulus
hrs	hours
HZ	Hertz
ICA	Independent Component analysis
ICC	Intra-Class Correlation
IPEG	International Pharmaco-EEG Society
LME	Linear Mixed-Effect
MADRS	Montgomery-Åsberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MDD	Major Depression Disorder
MMN	Mismatch Negativity
MoCA	Montreal Cognitive Assessment
morphology	Waveform features of the ERP, over time within the epoch
MRI	Magnetic Resonance Imaging
ms	Milliseconds
mTOR	mammalian Target Of Rapamycin
NART	National Adult Reading Test
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
Oddball task	Classic cognitive neuroscience paradigm to elicit P300
PD	Pharmacodynamic
PET	Positron Emission Tomography
PFC	Prefrontral Cortex
pharmaco-EEG	pharmaco-Electroencephalography
PING	Pyramidal-Interneuron Gamma

PK	Pharmacokinetic
PSD	Power Spectral Density
PTM	Post Translational Modifications
PTSD	Post-Traumatic Stress Disorder
qEEG	Quantitative EEG
rsEEG	Resting state EEG
RT	Reaction Time
SD	Standard Deviation
SE	Standard Error
SHAPS	Snaith-Hamilton-Pleasure-Scale
SME	Standardized Measurement Error
Sonic Scene	Gamified Mismatch Negativity Task developed by Cumulus
SSRI	Selective Serotonin Receptors Inhibitors
SUS	System Usability Scale
US	United-States
WHO	World Health Organization
WMS	Wechsler Memory Scale
µV	MicroVolts

IX Table of Contents

I Declaration 2
II Disclosure, funding, and conflict-of-interest 3
III Summary 4
IV List of Publications and Presentations 8
V Acknowledgements 10
VI List of Tables 12
VII List of Figures 14
VIII List of Abbreviations 25
IX Table of Contents 28
1 General Introduction 30
1.1 Current challenges of brain research 30
1.2 Gamification of standard laboratory paradigms for repeated remote testing 35
1.3 Electroencephalography 37
1.4 Remote dry EEG 43
1.5 EEG can detect drug action 50
1.6 Thesis overview and objectives 52
2 General Methods 55
2.1 Dry EEG datasets 55
2.2 The Cumulus platform 63
3 Empirical Chapter 1 72
3.1 Introduction 73
3.2 Methods 75
3.3 Results 80
3.4 Discussion 109
4 Empirical Chapter 2 113
4.1 Introduction 114
4.2 Methods 120
4.3 Results 127
4.4 Discussion 169
5 Empirical Chapter 3 171
5.1 Introduction 172

5.2 Methods 174
5.3 Results 179
5.4 Discussion 285
6 General Discussion 287
6.1 Summary of findings 287
6.2 General discussion 289
6.3 Limitations 298
6.4 Relevance for future directions 302
7 Conclusion 307
8 Appendix 309
8.1 System Usability Scale 309
8.2 Empirical chapter 2 : Ketamine metabolites analyses 310
9 References 312

1 General Introduction

1.1 Current challenges of brain research

1.1.1 Obstacles to large scale data collection

The traditional way of collecting neurocognitive and brain data, where researchers and clinicians invite participants at the laboratory or clinic to supervise all the recordings is inefficient and resource-intensive, which precludes large scale data collection. Trained experimenters need to be present to supervise recordings and institutions need to have access to research facilities to run their experiments and welcome participants. Due to these practicalities, laboratories are limited in the number of people they can test for a given study. There is also a limit to the number of participants that are willing and/or have the capacity to come to the laboratory in-person, leaving certain clinical populations and minorities out-of-reach. As a result, large scale studies typically take months or years to complete and a large percentage of participants are students and not therefore representative of the general population (Sears, 1986; Kam, Wilking and Zechmeister, 2007; Henrich, Heine and Norenzayan, 2010).

A second obstacle to scaling up cognitive neuroscience is the high cost of neuroimaging technologies, which make them inaccessible to many laboratories and research centres (Geethanath and Vaughan, 2019). In 2017, a report from the World Health Organization (WHO) revealed that over 95% of low-income countries did not have access to Positron Emission Tomography (PET) scanners and >50% of all the countries of the world still did not have at least one Magnetic Resonance Imaging (MRI) unit (Geneva: World Health Organization, 2017). The total costs for a state-of-the-art 3T MRI scanner can easily exceed $2M to which must be added an additional $0.75M to $1.0M for site preparation and construction (Simonetti and Ahmad, 2017). The price of a PET scan can go up to $1,400 (Keppler and Conti, 2001). A consequence of this is that their repeated use in research is unrealistic. Finally, even when sufficient resources are

available, studies have revealed scanner-dependent structural findings and warned against the reliability of structural imaging when tested across scanners (Keppler and Conti, 2001; Kruggel, Turner and Muftuler, 2010). As a result, complex harmonisation procedures needs to be put in place to enable the cross-sectional analyses of dataset collected across multiple recruiting sites which further complicates the large scale use of neuroimaging technologies (Dewey *et al.*, 2019). Ideally, biomarkers should be robust to the variability of the technology used to make the measurements, and the intraindividual variability unrelated to clinical state (Linden, 2012). All these observations taken together suggest that there is a critical need to develop new approaches to collect meaningful neurocognitive and brain data truly informative of brain disorders.

1.1.2 The importance of longitudinal recordings to study brain disorders

The material and logistical barriers to large scale brain data collection have precluded the generation of datasets which are both large (in terms of N) and longitudinal. The scientific consequence of this problem is that the examination of variation either within or across individuals have been overlooked to some extent. Measuring brain activity at a single time point in time may not provide data that reflects a person's typical neurocognitive performance, thereby limiting the replicability of findings (Aarts *et al.*, 2015; Baker, 2015; Bohannon, 2015). Lifestyle factors, mood, stress and energy levels affect behaviour and cognitive functioning (Dustman *et al.*, 1990; Barry *et al.*, 2005; Brose *et al.*, 2012; Shochat, 2012; Brose, Lövdén and Schmiedek, 2014; Fleck *et al.*, 2019). For example, when the aim is the classification of an individual, data from a single recording session can prove misleading if the person was especially tired or distracted on the day of testing. In that case, both behavioural and brain data can be affected and become unrepresentative of the targeted brain processes. Testing repeatedly over weeks or months can correct this bias by allowing a user to accumulate enough data for a personal baseline metric of cognitive performance, which accounts for daily variation in lifestyle and circumstances (Figure 1) (Rast, MacDonald and Hofer, 2012).

Figure 1: **Schematic representation of fluctuation in cognitive functioning across time.** Schema adapted from Sliwinski and Hassenstab.

Beyond the question of the validity of the data captured, collecting data over a longer time scale is also critical when looking at slow-developing neuropsychiatric conditions. The incubation period of neurodegenerative disorders is typically within the range of years. For instance, the characteristic average time frames of the early, middle and severe stages of Alzheimer's Disease (AD) range from 2 to 4 years, 2 to 10 years, and 1 to 3 years respectively (Burns and Iliffe, 2009). The detection and treatment of cognitive illness onset is likely to be more effective when monitoring brain activity over the long-term.

Likewise, the action of drugs on the central nervous system can take some time to build to therapeutic effect. Selective Serotonin Receptors Inhibitors (SSRIs) used for the treatment of major depression and anxiety disorders, exhibit therapeutic effects only after 1 or 2 months of treatment (Dumont *et al.*, 2005; Bares *et al.*, 2017; Dohrmann *et al.*, 2017; Widge *et al.*, 2019). Even though SSRIs have been available for more than 30 years, their exact mechanisms of action remain unknown. To unravel the underlying mechanisms of either drug action or a neuropsychiatric condition, multiple biological processes must be examined together – each occurring at a different pace. At the cellular level, the modulation of an action potential typically occurs within the millisecond range while protein synthesis dependent neuroplasticity happens across multiple days. Modification of brain region connectivity which takes place during learning

and long-term memory consolidation can take up to several weeks or months. Neurodegeneration, as mentioned before, happens over years. Hence, the development of a new neuroimaging platform that enables massive-scale longitudinal recording within the same individuals, and across cognitive groups, could yield heretofore unknown biomarkers of brain functioning.

The two major constraints preventing longitudinal collection of data from the same individuals are simple practical concerns: testing sessions are time consuming and expensive. It is not realistic to expect trial participants to attend sessions in-laboratory several times per week, nor to employ numerous researchers to visit participants in their homes. Thus, longitudinal data collection from large numbers of people is only feasible if individuals can perform testing and collect data autonomously and at low cost.

1.1.3 The growing interest in remote research

1.1.3.1 Fully Remote Research: Online crowdsourcing services

A growing body of research is looking at new ways of recording brain data that could address the problems detailed above. A promising avenue is the development of remote tools and platforms where experimenters are no longer required to conduct experimental testing and supervise recordings. At the conceptual level, enabling research participants to self-administer their tests is very attractive as it would reduce study costs, decrease experimenter-introduced bias, make it possible to multiply both the number of samples collected and participants enrolled, and enable reaching remote populations with richer diversity profiles (Chandler and Shapiro, 2016a; Lau-Zhu, Lau and McLoughlin, 2019). Remote research can be achieved through different methods, but the most popular ones include online data collection tools and connected devices. Online data collection tools such as online crowdsourcing services have recently been investigated as an alternative way of collecting behavioural datasets (Crump, McDonnell and Gureckis, 2013; Chandler and Shapiro, 2016b; Zhou and Fishbach, 2016; Chandler and Paolacci, 2017). Online collection may address several of the problems highlighted by opening research to more various

and larger pools of participants. Automated paradigms may additionally remove unintended but systematic effects associated with specific experimenters. The feasibility of conducting such research has already been demonstrated by the successful completion of multiple research projects (Mason and Suri, 2012; Shapiro, Chandler and Mueller, 2013; Chandler and Shapiro, 2016a). The validity of the data collected remains an active topic of discussion (Oppenheimer, Meyvis and Davidenko, 2009; Paolacci, Chandler and Ipeirotis, 2010a; Zhou and Fishbach, 2016; Chandler and Paolacci, 2017) although recent research seems to suggest that aggregates of multiple unsupervised assessments delivers levels of reliability comparable to what is observed in controlled environment (Brown *et al.*, 2014; Lipsmeier *et al.*, 2018; Sliwinski *et al.*, 2018).

1.1.3.2 Semi-remote approaches

Semi-remote approaches consist in inviting research participants at the laboratory/clinic at the study start to introduce them to the protocol and provides them with the specialized hardware needed to autonomously collect data in the home (see (McWilliams *et al.*, 2021) for an example of a semi-remote study). This approach is an attractive alternative to fully remote studies as researchers and participants can meet and build a connection which can later positively influence adherence to study protocols (Moore *et al.*, 2021). Participants become acquainted with the research team and can ask their questions in person. Then, the researchers provide them with the specialised hardware and can conduct additional in-person test and assessments if desired. This approach also addresses some of the problems reported in fully remote research where for example, participants may sometimes enrol in studies without meeting inclusion criteria (Chandler and Paolacci, 2017). Meeting the participants at enrolment enables the research team to verify their suitability for the given research. Further, it allows for the standardization of the hardware used as letting the participants use their personal device can introduce noise in the samples if the device sampling rates vary significantly (Crump, McDonnell and Gureckis, 2013; Nicosia, Wang, *et al.*, 2022).

1.2 Gamification of standard laboratory paradigms for repeated remote testing

1.2.1 Validity of unsupervised experiments completed in ecological environment

In addition to the collection of data via surveys and questionnaire, an essential part of psychology research relies on the administration of neurocognitive behavioural paradigms to participants. In traditional research settings, the experimental conditions in which the tasks are being conducted are controlled by the researchers. One challenge associated with remote testing is the lack of control over the conditions in which the tests are completed (Chandler and Shapiro, 2016a; Nicosia, Aschenbrenner, Balota, *et al.*, 2022). Participants may be interrupted during their session (e.g., phone calls), not comply with task instructions, or get distracted and start doing other things while doing the tests, such as attending to a television or a radio in the background (Paolacci, Chandler and Ipeirotis, 2010b; Chandler and Shapiro, 2016a). To evaluate the extent of the problem, studies have looked at the validity and reliability of behavioural data collected remotely without supervision and initial results are promising. Crump and colleagues successfully replicated multiple tasks from experimental psychology delivered via Amazon Mechanical Turk (AMT), an online crowdsourcing service where anonymous online workers complete web-based tasks (Crump, McDonnell and Gureckis, 2013). Another AMT study published test-retest reliability coefficients ranging between 0.8 to 0.94 (Buhrmester, Kwang and Gosling, 2011). In a smartphone-based study, Thompson et al. reported excellent within-person reliability scores ranging from 0.89 to 0.97 using a mobile app-based cognitive testing platform (Thompson *et al.*, 2022). Taken together, these results suggest that remote testing is a valid approach to collect quickly and inexpensively meaningful data informative of variety of brain cognitive functions.

1.2.2 Gamification of laboratory paradigms to facilitate repeated testing

Traditional cognitive laboratory tasks and paradigms have been designed to test groups of individuals once or twice only. The possibility of testing in the home over extended periods comes with a new set of challenges, including the necessity of keeping people engaged over extended

periods of time. The critical need of maintaining a good level of engagement from participants is twofold: i) quantity: to collect the large volume of data required for capturing subtle changes and for powerful machine-learning techniques (Gillan and Whelan, 2017), participants should be inclined to complete the sessions and adhere to study protocols; ii) quality: at-home recordings are unsupervised and if participants are not adequately engaged, the data collected could be unrepresentative of the targeted brain processes. Traditional experimental paradigms, though they allow for the extraction of meaningful metrics of cognition, are not designed for repetitive use and can become quite tiresome if administered multiple times (Lumsden *et al.*, 2016). Neurocognitive tasks commonly used in EEG research typically require sustained attention for extended periods (e.g., 20 mins). During this time, participants are often asked to respond to simple geometric stimuli presented on a uniform background screen, with deliberately little variation among trials. Previous reports of in-home monitoring devices have shown that maintaining adherence over time with these tasks is challenging (Chaudhry *et al.*, 2010; Ong *et al.*, 2016). This can lead to elevated attrition rates, which reduces sample sizes, wastes participant effort, and biases results (Dumville, Torgerson and Hewitt, 2006). Gamification of laboratory paradigms – adding game-like features (points, graphics, levels, storyline, etc.) – could address these problems by keeping study participants engaged while their cognition and brain activity are repeatedly sampled (Prins *et al.*, 2011; Sailer *et al.*, 2014; Lumsden *et al.*, 2016; Sardi, Idri and Fernández-Alemán, 2017). For example, a gamified behavioural spatial memory task administered longitudinally was more effective at classifying at-high-risk AD healthy participants than traditional neuropsychological episodic memory tests (Coughlan *et al.*, 2019).

1.3 Electroencephalography

1.3.1 What is Electroencephalography?

Electroencephalography (EEG) is a non-invasive electrophysiological technique used to record and monitor brain activity (Teplan, 2002; Light *et al.*, 2010). More specifically, EEG measures voltage fluctuations resulting from the ionic current of neurons located near the surface of the brain. The human brain naturally produces electrical impulses fluctuating in rhythmic patterns, creating so-called 'brain waves' (Teplan, 2002; Light *et al.*, 2010). These patterns, if examined properly, can deliver key information on the current brain state and functioning of an individual. In clinical settings, EEG has traditionally been used to diagnose diverse neurological disorders such as epilepsy, encephalopathy or sleep disorders (Michel and Brunet, 2019). It can be used either to measure large-scale spontaneous oscillatory activity in neural populations, particularly during quiet wakefulness, or time-locked to a stimulus or task. EEG recorded at the surface of the head only measures superficial voltage potentials induced by brain cells upon activations (Teplan, 2002; Light *et al.*, 2010). When a neuron gets activated, an electrical current is produced via the transport of charged molecules across the cell membrane and this current is then propagated to other neurons via complex molecular mechanisms. EEG technology can only capture the activation of large population of neurons firing together (Assenza and Lazzaro, 2015). It is thought that EEG signals come from populations of pyramidal neurons located in the cerebral cortex. When a group of neurons fire together, the sum of their graded potentials creates an electrical dipole that is captured by the electrodes.

EEG technology sets itself apart from other neuroimaging technology by its high temporal resolution, within the range of milliseconds, its safety of use – not involving exposure to radioactive isotopes or ultra-high intensity magnetic fields, and its lack of requirement for highly controlled magnetically shielded environment. Because of these characteristics, EEG is an excellent candidate for large scale commercialization and distribution to enable to remote collection of brain activity. It is a technology that can be delivered as a low-cost wearable

technology and provide objective measurement of the integrity of brain activity. Disruption of resting state activity and connectivity, especially slowing and attenuation of alpha rhythms, is for example a characteristic feature of dementia seen in "quantitative" EEG (qEEG) analyses (McMackin *et al.*, 2019; Babiloni *et al.*, 2020). Quantitative EEG provides additional discriminative power even in the context of a state-of-the-art diagnostic work-up that already includes molecular biomarkers and neuroimaging (Ferreira *et al.*, 2016; Koenig, Smailovic and Jelic, 2020).

1.3.2 Resting State EEG

Resting state EEG (rsEEG) corresponds to the measure of large-scale oscillatory neural population spontaneous activity during quiet wakefulness. It may be particularly useful as a scalable method as it is a passive task, thus limiting the risk for a lack of adherence to task instructions. The evaluation of brain activity at rest is typically done by evaluating spectral power across five frequency bands: Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-30 Hz), and Gamma (30-200 Hz) (Buzsáki and Watson, 2012). The role and function of each band is still an area of active debate, but it is thought that specific behavioural states and cortex areas are associated with certain frequency bands (Buzsáki and Watson, 2012). For example, alpha activity has been classically described as an "idling rhythm" reflecting a relaxed, inactive mental state. However, more recent findings confirmed that internal tasks such as mental calculation, short-term and working memory or visual-spatial mental imagery exercises strengthen the alpha activity (Vaitl *et al.*, 2005; Klimesch, Sauseng and Hanslmayr, 2007; Palva and Palva, 2007; Lutz, Dunne and Davidson, 2012). The beta rhythm was found to be involved both motor and cognitive processes (Schmidt *et al.*, 2019) while gamma oscillations have been linked to sensory processing and cognitive impairment (Başar, 2013). Theta activity has been described as an index of mental workload and connected to working memory, executive control, and focused attention (Sauseng *et al.*, 2010; Herweg, Solomon and Kahana, 2020). Finally, delta waves have been associated with signal detection, and decision-making as well as emotional processes (Güntekin and Başar, 2016).

1.3.3 Event related Potentials – ERPs

When time-locked to an event, the electrical potentials recorded via EEG are called event-related potentials (ERPs) that can reveal – with temporal resolution in the range of milliseconds – the neural correlates of early sensory processes and of higher cognitive functions such as decision-making, episodic and working memory or executive function (Light *et al.*, 2010; Babiloni *et al.*, 2020). They are extensively explored in cognitive and behavioural neuroscience, cognitive psychology, and psychophysiological research. Measures of task-driven EEG can provide additional precision in cognitive assessment as to the domain specificity of network damage, for instance, when differentiating Alzheimer's type dementia (where memory is prominent in early impairments) from Parkinsonian or Fronto-Temporal dementias (where executive function may be the first domain to be compromised) (Nardone *et al.*, 2018). Further, it is thought that cognitive paradigms taxing specific domains could be more informative compared to resting state recordings when building predictive models of fluid intelligence (Greene *et al.*, 2018). Task-driven EEG can also discriminate between different stages of cognitive processing (e.g., attention, sensory processing, decision making, motor preparation and execution), which are typically conflated in a single behavioural output such as response accuracy or reaction time (Twomey *et al.*, 2015).

1.3.3.1 The P300 and Oddball paradigms

The active Oddball task is one of the most ubiquitous tasks in cognitive neuroscience (Herrmann and Knight, 2001). The EEG measure that it yields, the P300 (more specifically the P3b variant) has been implicated as a marker of cognitive impairment in a range of pharmacological and patient population studies (Twomey *et al.*, 2015; Schwertner *et al.*, 2018). The P300 ERP is thought to reflect decision making and context-updating processes (Twomey *et al.*, 2015), attention reallocation (Linden, 2005), and seems particularly promising for detecting cognitive decline (Horvath *et al.*, 2018; Babiloni *et al.*, 2020; Paitel, Samii and Nielson, 2021), with the benefit of being robust to education (Pavarini *et al.*, 2018). It is a widely studied ERP that is often evoked

using auditory Oddball tasks, during which participants should attend to the presence of an infrequent stimulus (Dinteren *et al.*, 2014). It consists of a positive deflection occurring from approximately 300ms after presentation of the infrequent stimulus (Polich and Kok, 1995; Linden, 2005). The P300 observed following target stimuli is typically larger than that observed following non-target stimuli. This paradigm can be implemented either with auditory or visual stimulus. In the latter case, the participant must watch out for a target stimulus and respond as quickly as possible when it appears on-screen. Targets are typically presented relatively infrequently; non-targets make up as many as 80-90% of stimuli.

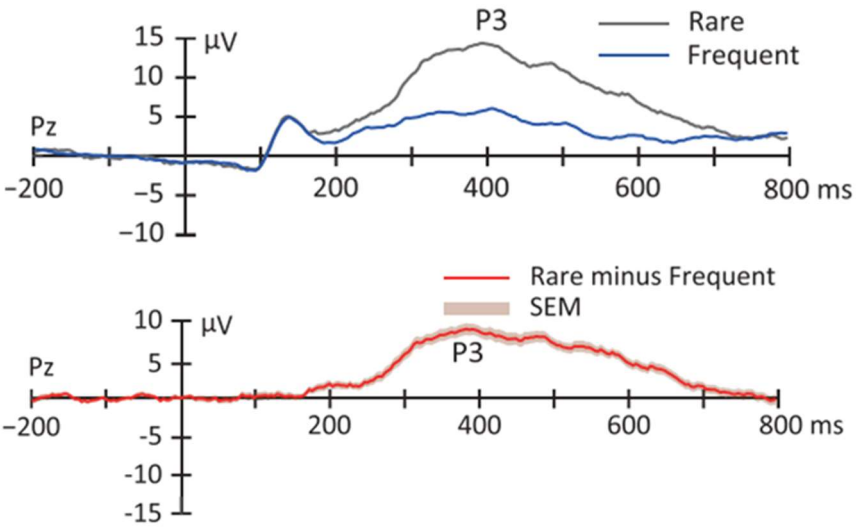


Figure 2: Canonical P300 ERPs from the ERP Core open-source dataset. ERP image from (Zhang and Luck, 2023). Top Panel: Grand average ERPs extracted from Rare and Frequent trials. Bottom Panel: Difference waves. The original figure was released under a CC BY license (http://creativecommons.org/licenses/by/4.0/).

1.3.3.2 The Mismatch Negativity

In contrast to the P300 ERP, which requires an active response, the mismatch negativity (MMN) ERP is produced by passive auditory Oddball paradigms in which a train of frequent tones are

interspersed with rare ('deviant') tones differing in duration or frequency (Näätänen *et al.*, 2011). This is a fronto-central difference wave ERP elicited by infrequent 'deviant' stimuli in a train of 'standard' stimuli. Stimuli are usually synthesised 'beeps' delivered around once every second (Kathmann, Frodl-Bauch and Hegerl, 1999). ERPs are more negative following deviant stimuli (Kathmann, Frodl-Bauch and Hegerl, 1999). The task is performed passively – the subject merely needs to remain still while listening to repetitive auditory stimuli. 10-20% of these bleeps are different in some perceptible way – in pitch, duration or loudness. The subject must be distracted from paying attention to the sounds, and a typical laboratory implementation of the MMN paradigm has subjects watching a silent film, or reading on-screen text (Duncan et al., 2009). The MMN ERP is thought to reflect automatic sensory processing and to act as a perceptual prediction error signal, with a latency of 100-200ms post deviant stimulus presentation and ERP amplitude maximal at frontocentral sites (Lindín *et al.*, 2013).

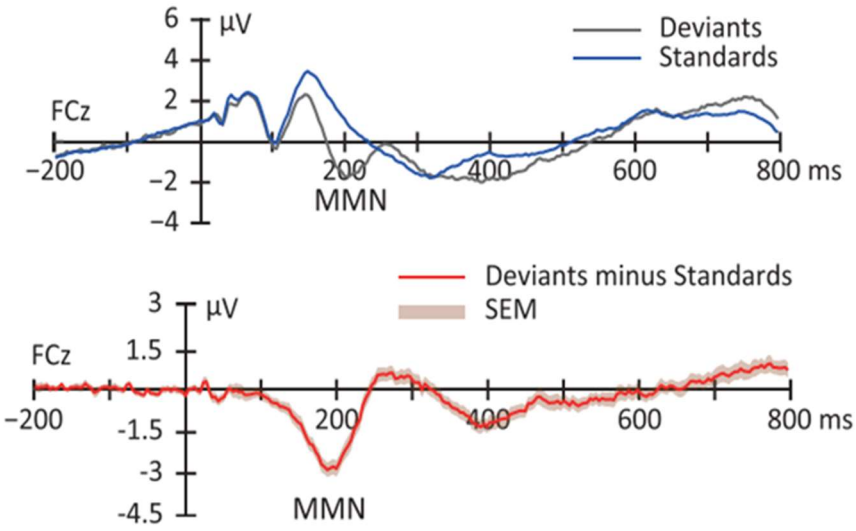


Figure 3: Canonical MMN ERPs from the ERP Core open-source dataset. ERP image from (Zhang and Luck, 2023). Top Panel: Grand average ERPs extracted from Deviants and Standards trials. Bottom Panel: Difference waves. The original figure was released under a CC BY license (http://creativecommons.org/licenses/by/4.0/).

1.3.3.3 The Error-Related-Negativity (ERN)

Another widely studied ERP is the error-related negativity (ERN) (Olvet and Hajcak, 2009; Gehring *et al.*, 2018). It is typically elicited during the Flanker task during which participants respond to the direction of a central stimulus surrounded by an array of stimuli, which point in the same ('congruent') or the opposite direction ('incongruent'). The Flanker task is commonly used in cognitive psychology to evaluate the ability of an individual to suppress behavioural responses inappropriate to a particular context (Erb, Touron and Marcovitch, 2020). It requires the subject to respond to the orientation of a central stimulus – which typically points left or right, surrounded by an array of 'distractor' stimuli i.e., flankers, which should be ignored. Flankers are far more numerous than the central target stimulus, and ignoring them can represent a meta-cognitive challenge, especially when the subject is instructed to respond as fast as possible. The subject's ability to inhibit the incorrect response on incongruent trials is a cognitive marker of inhibition (Erb, Touron and Marcovitch, 2020). This task is especially relevant to examine processes related to attention and error monitoring, and so executive function more broadly (Yeung, Botvinick and Cohen, 2004). The ERN consists of a negative voltage deflection observed fronto-centrally that occurs around the time of an incorrect response. It is characteristically followed by a positive rebound in the signal, known as the Error Positivity (Pe), which is more posterior than the ERN. The ERN is thought to reflect an adaptative response strategy when post-response conflicts are detected (Nieuwenhuis *et al.*, 2001; Yeung, Botvinick and Cohen, 2004; Davelaar, 2013) and attentional control processes are engaged (Yeung, Botvinick and Cohen, 2004), while the Pe has been linked to conscious error recognition (Nieuwenhuis *et al.*, 2001; Olvet and Hajcak, 2009; Yeung and Nieuwenhuis, 2009).

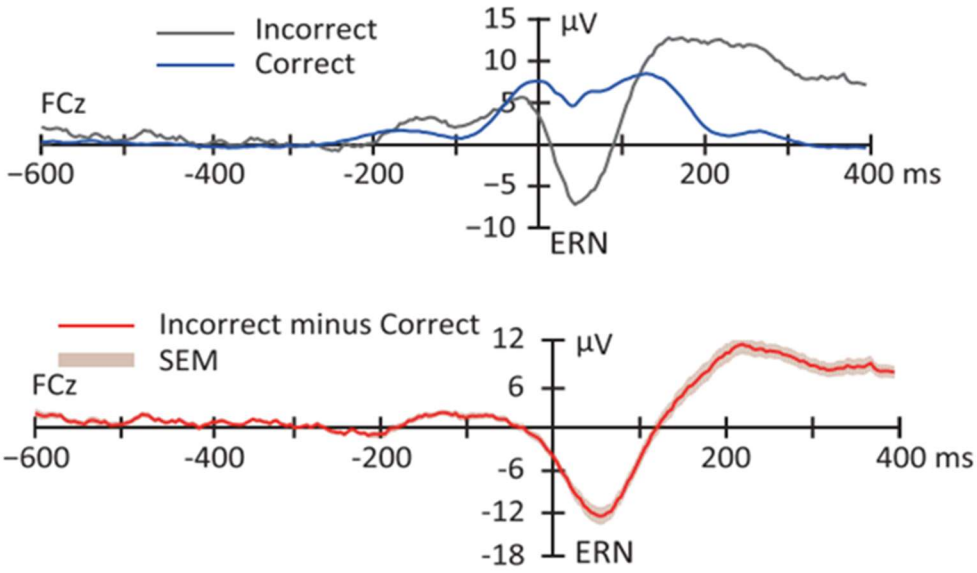


Figure 4: Canonical ERN ERPs from the ERP Core open-source dataset. ERP image from (Zhang and Luck, 2023). Top Panel: Grand average ERPs extracted from Incorrect and Error trials. Bottom Panel: Difference waves. The original figure was released under a CC BY license (http://creativecommons.org/licenses/by/4.0/).

1.4 Remote dry EEG

1.4.1 From wet to dry electrodes

Traditional wet EEG set-ups are composed of a set of electrodes, a headcap with placeholders for positioning the electrodes, a battery, an analogue-to-digital converter and some amplifiers with filters (Teplan, 2002; Light *et al.*, 2010). The headcap holds the electrodes onto the scalp at fixed positions while neuronal activity is captured in the form of a voltage potential. This signal is then amplified and converted into a digital signal by the analog-to-digital converter and finally sent to a laptop or computing device for analyses and storage. When performing wet EEG, the experimenter must manually apply conductive gel or paste between each electrode and the scalp to ensure good contact between the skin and the sensors for adequate signal quality (Light *et al.*, 2010). The number of electrodes used during a recording can greatly vary depending on the tasks

performed and experimental objectives, but it typically ranges from a couple up to 256 sensors. A classic in-laboratory session lasts at minimum a couple of hours and is quite labour intensive for both the experimenter and participant. It is generally led by one or two qualified technicians and include the following steps:

1. First the participant's head measurements are captured, and the participant is fitted with the adequate cap.
2. Second, before placing the electrodes onto the headcap, the experimenters must apply a conductive gel/paste onto the skin of the participant/patient at each sensor location. For high density cap such as the ones including 128 or 256 sensors, this step can take up to 20 or 30 mins during which the participant is restricted in movements.
3. After applying the gel, the experimenter must manually place the electrodes onto the cap. As before, this step is manually done for each sensor. Some wet EEG systems make use of ring electrodes inside which the conductive gel can be directly applied. In that case, this step may be completed simultaneously as step 2.
4. Once the electrodes are in place, the experimenter must verify the contact quality of the set-up and correct for any misplacement.
5. Finally, once the system has successfully been checked, the recordings can start.

This way of performing clinical and basic research works and have been extensively used during the last 50 years but it has fundamental drawbacks. Recording sessions are burdensome both for the experimenter and study participant and require technicians with substantial expertise in EEG (Di Flumeri *et al.*, 2019). Advances in EEG sensor development, signal processing, and cloud-based technologies have enabled the creation of wireless, dry EEG recording systems that can be operated repeatedly by naïve users unsupervised in the home (Hairston *et al.*, 2014; Maskeliunas *et al.*, 2016; Krigolson *et al.*, 2017; Lau-Zhu, Lau and McLoughlin, 2019; McWilliams *et al.*, 2021; Barbey *et al.*, 2022). 'Wet' and 'Dry' refer to the type of electrodes used to conduct the signal from

the scalp: the former requires a conductive medium (electrolytic gel or water) whereas the latter relies on mechanical pressure against the scalp to ensure contact.

The main advantage of using dry electrodes lies in the fact that experimenters do not have to put gel between the skin and the electrodes which considerably shortens the recording preparation time, saves participants from having to wash their hair, and prevents variation in electrode impedance due to gel drying (Lin *et al.*, 2011; Di Flumeri *et al.*, 2019). When dry electrodes are coupled with a wireless system, it also saves participants from having perhaps >100 of cables connected to their scalp which makes the experience more ecologically valid and comfortable. It can take up to an hour for an EEG technician to prepare a wet cap before, and to clean it after, a recording session. This work needs to be repeated for every single recording session of a study. If we take the example of a 30-participant study involving 1 hr of task-driven EEG recordings, it means that a trained technician must administer over 600 hrs of recordings. Using a dry EEG system, the same quantity of recordings could be collected in 300 hrs, and after that, participants could go home with the hardware and provide dozens more sessions without supervision. In this scenario, dry EEG studies would cost a fraction of a wet EEG study and yield dataset possibly ten times larger. Automated data collection from the home also enables the collection of data in a more ecologically valid way as participants are performing testing sessions in a familiar environment where no bias may be introduced by either the laboratory context or the experimenters themselves (e.g., such as the “white coat effect”) (Barber and Silver, 1968; Mario *et al.*, 2009; Leach *et al.*, 2020).

Figure 5: Electroencephalography recording set-up. Left panel: 128-channel Biosemi wet EEG recording set-up. Right Panel: Portable wireless Cumulus Dry EEG set-up.

1.4.2 Technical characteristics of dry and wet EEG electrodes

Each electrode type has specific technical characteristics that will impact the quality of the signals recorded. Some of the features examined when looking at electrode performance include their impedance, active or passive nature, and susceptibility to noise sources (Habibzadeh Tonekabony Shad, Molinas and Ytterdal, 2020). Active electrodes, as opposed to passive ones, are associated with a pre-amplification module that allows the amplification the signal at source before noise contamination and are, therefore, more robust to noise and external contamination. The impedance of an electrode is the opposition of the electrode to alternating currents. By definition, the higher the impedance of an electrode is, the more it will prevent the passage of the current and of EEG signals. Conventional wet electrodes typically exhibit low impedance (usually below 5kOhms) as the addition of gel or saline solution greatly improve the connection between the skin and the electrodes (Fiedler *et al.*, 2014; Xu *et al.*, 2017; Habibzadeh Tonekabony Shad, Molinas and Ytterdal, 2020). Reports on dry electrodes impedance have shown that it varies according to several factors including electrode coating, placement, shape and number of pins, as all of these impacts contact surface with the skin and the conduction of the signals (Fiedler *et al.*, 2014, 2015, 2018; Wang *et al.*, 2016). Fiedler and colleagues have extensively examined the multi-pin coated Ag/AgCl dry electrodes developed by Ant-Neuro that are currently used in the waveguard™ touch

EEG cap (Waveguard EEG caps, ANT B.V., Enschede, The Netherlands) and the Cumulus dry EEG headset (www.cumulusneuro.com). They reported, when embedded in the waveguard™ touch EEG cap, average impedances below 150 kOhms for 95% of the 97 electrodes of the cap (Fiedler *et al.*, 2015). They also conducted extensive contact pressure analyses that revealed that below a normal force of 1N (e.g., 0.4 kg/cm^2), the electrode impedances were highly variable ranging between 100 to 1200 kOHms. From 2N and above, multipin-shaped electrodes passed through the hair layer and reproducibly and reliably establish sufficiently low electrode-skin impedances (e.g., below 250 kOhms) that are compatible with state-of-the-art biosignal amplifiers (Fiedler *et al.*, 2018).

Another important technical feature of EEG recording device is the common mode rejection ratio (CMRR). It refers to the capability of a recording set-up to reduce the amplification of common mode signals. The common mode signal or common mode interference refers to any external undesirable signal that would be captured by both the recording and reference electrodes. The CMRR quantifies an EEG device ability to reject this common mode interference. It is typically expressed in decibels and represents the ratio of the magnitude of the desired brain signal (differential mode signal) to the magnitude of the unwanted common mode signal. A higher CMR indicates better rejection of common mode signal, resulting in a cleaner and more accurate EEG signal. Active wet EEG systems can have CMRR as high as 90 dB (c.f. Biosemi technical sheet, https://www.biosemi.com/activetwo_full_specs.htm).

1.4.3 Validation of the approach

Wireless dry EEG holds much promise, but further validation of the approach is still required. Over recent years, there has been a proliferation of wireless, portable EEG recording systems which can be operated by naïve users unsupervised outside of the laboratory (Hairston *et al.*, 2014; Kuziek, Shienh and Mathewson, 2017; Lau-Zhu, Lau and McLoughlin, 2019; McWilliams *et al.*, 2021). Such devices are currently being tested in a wide range of use-cases including brain-computer interfaces (BCI) (Abiri *et al.*, 2020), epilepsy research (Biondi *et al.*, 2021), neurofeedback

interventions (Johnstone *et al.*, 2017; Al-Taleb *et al.*, 2019), sleep research (Arnal *et al.*, 2020), or for EEG-enhanced cognitive testing (Griffiths *et al.*, 2016; McWilliams *et al.*, 2021). New portable EEG systems vary on a wide range of parameters including the cap density and electrode placement, technology portability and user-friendliness, and whether the signals are transmitted wirelessly or via cables to analogue-to-digital converters (Lau-Zhu, Lau and McLoughlin, 2019). To ensure study protocol adherence and prevent high attrition rates, these devices must be easily usable by naïve user in unsupervised settings. Ideally, they should require no clean-up and minimal preparation from the subjects. For this reason, semi-rigid systems allowing the effortless and correct placement of electrodes on the scalp are preferred (Cruz-Garza *et al.*, 2017). The session duration also seems to be important, although no clear guidelines can be found and further investigations must be made to determine the ideal duration of at-home self-administered EEG recording sessions (Hairston *et al.*, 2014). The nomenclature for remote EEG reflects the variety of possible configurations (Bateson *et al.*, 2017). 'Portable' refers to any recording system which is designed to be used outside the laboratory. 'Mobile' refers specifically to technology which can be used while being in motion, such as walking or on a treadmill (Debener *et al.*, 2012).

It should be noted that most usability studies completed to date were conducted in laboratories and/or always overseen by trained technicians (Casson *et al.*, 2008; Hairston *et al.*, 2014; Radüntz, 2018; Kam *et al.*, 2019). Very few data are available on how participants behave when left to themselves in the home for extended periods of time. To the best of my knowledge, only one study looked at the feasibility of repeated cognitive function assessment in older adults via a wireless EEG platform from the home (McWilliams *et al.*, 2021). McWilliams and colleagues reported data from 89 older adults (aged 40 to 80 years) who were asked to complete 30-minute long at-home recordings 5 times a week for 12 weeks with minimum compensation. Their study revealed the feasibility of such an approach with a mean compliance of 82% (4.1 sessions per week) and an attrition rate of 12.4% (11 withdrawal out of 89 participants enrolled). Age did not seem to negatively influence participants' adherence to the study protocol and no drop in data

collection were observed at the end of the study. Finally, 96% of the sessions collected contained portions of EEG data that could be used for analysis (McWilliams *et al.*, 2021). These results are very encouraging regarding the feasibility of such an approach and suggest that it is possible to collect brain data from the home to evaluate cognition.

When looking at data quality, initial reports suggest that dry EEG devices yield data that are equivalent in quality to that captured via gold-standard traditional wet EEG technology, although a striking lack of consensus can be noted in the different evaluation methods used (Barham *et al.*, 2017; Mathewson, Harrison and Kizuk, 2017; Radüntz, 2018; Kam *et al.*, 2019; Hinrichs *et al.*, 2020). Headsets' performance are being assessed through correlations between wet and dry EEG signals (Kam *et al.*, 2019), direct wet-to-dry signals comparison via paired t-test (Hinrichs *et al.*, 2020), intra-class correlations (ICCs) computed across wet and dry signals (Badcock *et al.*, 2013; Barham *et al.*, 2017), ICCs and Coefficients of Repeatability (CRs) across different time points (Rogers *et al.*, 2016), and computation of a signal-to-noise ratio (Barham *et al.*, 2017; Radüntz, 2018). The wide variety of approach used non-systematically across different devices and manufacturers prevents us from reaching conclusions on the best device and systems to use but it shows that overall, dry EEG systems are now performing as well as wet EEG technology. Specifically, Hinrichs and colleagues reported paired t-tests results revealing no substantial differences (p-values >0.1) between wet and dry headset electrodes when evaluating amplitude and latencies of ERPs in 16 healthy subjects and 16 neurological patients (Hinrichs *et al.*, 2020). Kam and colleagues reported significant positive correlations (r = 0.54–0.89) between signals extracted from wet and dry EEG when evaluating spectral components as well as ERPs in 27 healthy volunteers (Kam *et al.*, 2019). When assessing the reproducibility of a dry EEG measurement using intra-class correlations (ICCs) coefficient, Rogers and colleagues reported that eye-closed resting state measurement were stable across three separate testing time points in youths (10-17 years old), adults (18 to 28 years old), and elderlies with ICCs ranging between 0.76

to 0.85 (Rogers *et al.*, 2016) matching what is found in the wet literature (Cassidy, Robertson and O'Connell, 2012).

Finally, task-driven EEG research relies on the capture of ERPs which add an extra layer of complexity to the recording system as it requires a precise synchronization between the recording device and the platform presenting the stimulus (Barham *et al.*, 2017). Emerging approaches to achieve this are the coupling of headsets to android tablets (Barham *et al.*, 2017; McWilliams *et al.*, 2021) or laptops (Kuziek, Shienh and Mathewson, 2017) for stimulus presentation. A few studies already demonstrated that it was possible to produce laboratory-quality ERP waveforms at the expected scalp topography for the N200, ERN, MMN and P300 ERPs using dry EEG setups (Griffiths *et al.*, 2016; Mathewson, Harrison and Kizuk, 2017; McWilliams *et al.*, 2021).

1.5 EEG can detect drug action

1.5.1 Pharmaco-electroencephalography

EEG has been used for several decades for the detection of pharmacological drug effects on the central nervous system (Jobert and Wilson, 2016). In 2012, The International Pharmaco-EEG Society (IPEG) presented updated guidelines for the recording and computerised evaluation of pharmaco-EEG data (Jobert *et al.*, 2012). The term pharmaco-electroencephalography (pharmaco-EEG) describe *"the quantitative analysis of the effects of substances on the central nervous system (CNS) by means of neurophysiological and electrophysiological methods*" (Jobert *et al.*, 2012). Historically, pharmaco-EEG has been used to detect therapeutic drug action (see (Simpraga *et al.*, 2017) for an example of drug effect detection study), classify psychotropic substances (Saletu, Anderer and Saletu-Zyhlarz, 2006) and assess drug-drug interactions or monitor side effects and toxicity (Barbanoj *et al.*, 2006). EEG technology combined with pertinent cognitive measurement can be instrumentalised into a drug uptake and action detection tool. Drug pharmacology and pharmacodynamics are often studied with high spatial resolution imaging tools such as PET or fMRI. These tools, though they are great to examine which brain regions are impacted by a drug

of interest, have very low temporal resolutions which prevents monitoring brain activity in real-time. Expanding the use of EEG technology in pharmacology is of great interest as it would allow one to analyse drug effects and study the relationships between pharmacodynamic (PD) and pharmacokinetic (PK) data using direct measure of brain activity of high temporal resolution.

1.5.2 Ketamine neurobiology

Ketamine is a drug that has been widely examined with EEG. It is a well-known psychoactive compound which has been studied as a human model for schizophrenia and as a possible alternative treatment for treatment-resistant patients suffering from Major Depression Disorder (MDD) (Umbricht *et al.*, 2002; Honey *et al.*, 2006; Howland, 2013; Caddy *et al.*, 2014; de la Salle *et al.*, 2016). Several groups have already isolated EEG-biomarkers related to the uptake of ketamine in healthy and diseased populations relying on the known sensory modulations associated with the drug. One perceptual ERP in particular, the MMN, has been shown to be a reliable index of ketamine uptake within both animals and human research (Oranje *et al.*, 2000; Umbricht *et al.*, 2002; de la Salle *et al.*, 2016; Ahnaou *et al.*, 2017).

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate receptor (NMDAR) that has been commonly used as an anaesthetic and analgesic with excellent safety characteristics for more than 50 years. It has been approved in 2019 by the Federal Drug Agency (FDA) of the United-States (US) as a fast acting anti-depressant because of its putative upregulating effect over the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) trafficking and positive impact on neuroplasticity in mood relevant brain regions (Maeng *et al.*, 2008; Zanos *et al.*, 2016; Nugent *et al.*, 2019). A prominent hypothesis for its anti-depressant action is that it induces rapid increases in the transmission of glutamate at the synaptic cleft between interneurons and glutaminergic neurons (Walter, Li and Demenescu, 2014). This increase in glutamate seems to trigger an augmentation of the AMPAR trafficking in the postsynaptic neurons which in turn promote the synthesis of brain derived neurotrophic factor (BDNF) and synaptic proteins (Maeng *et al.*, 2008; Li *et al.*, 2010, 2017), including α-tubulin post translational modifications (PTMs) (Colic

et al., 2018). A number of preclinical and clinical studies showed that brain α-tubulin PTMs are altered in CNS disorders associated with major deficits in synaptic plasticity, including MDD (Bianchi and Baulieu, 2012). Microtubule dynamics can be analysed by measuring the post-translational modifications (PTMs) of the α-tubulin protein (i.e. acetylation) and represent a valid synaptic/cytoskeletal proteins biomarker of synaptic plasticity in the blood (Bianchi and Baulieu, 2012).

Patients suffering from MDD typically exhibit abnormal neuroplasticity patterns; inadequate BDNF secretion in brain regions associated with emotional processing such as the hippocampus; and deficits in glutaminergic activity in the anterior cingulate cortex (ACC - also involved in emotional processing); (Krystal, Sanacora and Duman, 2013; Walter, Li and Demenescu, 2014; Abdallah *et al.*, 2015; Sanacora *et al.*, 2017). At the same time, the modification of synaptic plasticity has been proposed as a potential treatment for a series of neurological disorders including chronic pain (Niesters, Martini and Dahan, 2014; Cohen *et al.*, 2018), post-traumatic stress disorder (PTSD) or migraine (Afridi *et al.*, 2013)(Afridi *et al.*, 2013). As such, ketamine seems to be an ideal candidate for the development of a fast-acting anti-depressant.

1.6 Thesis overview and objectives

The way brain and cognitive scientists have been collecting brain data over the last few decades has fundamental drawbacks. The cost of brain-sampling technology and the necessity of having participants visiting the laboratory to perform brain recordings prevent large scale data collection. The overarching objective of this thesis is to explore a new way of collecting brain data where participants are given easy-to-use hardware and software to conduct self-administered unsupervised recordings in the home. A range of devices and tools are becoming available that can make this possible (Hairston *et al.*, 2014; Lau-Zhu, Lau and McLoughlin, 2019). In this thesis, I used the neurocognitive platform developed by Cumulus Neuroscience Ltd

(www.cumulusneuro.com) which is indicative of this kind of approach. The Cumulus platform consists of a wireless dry EEG headset coupled with an android tablet for task presentations, and of a mobile app delivering a suite of gamified neurocognitive tasks. During their enrolment visit at the clinic or laboratory, study participants are taught how the use the mobile app and dry EEG headset by the study staff, and thereafter are sent home with the platform to complete recordings autonomously. The three empirical chapters (hereafter referred to as 'Empirical Chapter 1-3') of this thesis used a variety of experimental and analysis methods to validate and characterize the performance of such an approach and the diverse aspects of the platform:

Empirical Chapter 1 was focused on demonstrating the validity of the platform when dry-EEG, cognitive task gamification, and unsupervised home-based recordings are used in combination. Data were analysed from two different studies where younger and older adults used the Cumulus platform over several weeks in the home. The usability and feasibility of the platform were evaluated via participant adherence, percentage of sessions successfully completed, and quantitative feedback on the platform. After that, the quality of the at-home unsupervised self-administered dry EEG was evaluated and compared to the quality of wet supervised EEG recordings. To do so, I computed an established metric of signal variability within the field on our datasets and on an open-source wet EEG dataset taken from the literature.

Empirical Chapter 2 was a use-case study of the platform when deployed within the context of a pharmacological study. This was a placebo-controlled, double-blind, randomized, cross-over study designed to investigate the acute and persistent effects of ketamine on EEG and behavioural measures. The primary objective of this study was to evaluate if supervised dry EEG in the laboratory could capture the well-known acute effects of ketamine on brain activity and cognition as described in the wet EEG literature. The second objective of this study was exploratory and evaluated if at-home unsupervised self-administered dry EEG could capture persistent effects of a low dose of ketamine on brain activity and cognition. Intravenous infusions of racemic ketamine (0.5mg/kg) and saline were administered to 30 neurotypical adult males at the clinic on two

different occasions and participants completed two-weeks of at-home measurements before and after each infusion.

Empirical Chapter 3 aimed at evaluating the general construct validity of repeated gamified cognitive task administration to assess cognitive function. To do so, I conducted a deep evaluation of a gamified visual Oddball task to verify if the same electrophysiological correlates were elicited by the gamified task compared to what is reported in the literature of traditional Oddball EEG paradigms. This was done by conducting repeated measurements in a cohort of 10 healthy adults who completed 19 recordings either in the laboratory or in the home. The brain data described in this chapter were recorded using a standard wet EEG system as the objective of this study was to explore the validity of cognitive task gamification in isolation of the rest of the platform. Analyses were focused on the morphology, topography, and latencies of the brain signals elicited by the gamified task. After that, I evaluated the impact of repeated measurement on the brain and behavioural metrics of interest. This validation step aimed at discovering if the gamified task was still eliciting the brain signals of interest after numerous administrations.

2 General Methods

Some of the methods and tools used in this thesis are shared across several empirical chapters and different analyses. These are described here to avoid repetitions and will be referred to throughout the thesis.

2.1 Dry EEG datasets

Two dry EEG datasets were analysed within the context of this thesis. Details of the specific aims and analytical methods used for each chapter are detailed later in the relevant sections. I describe here the participants' recruitments and studies' procedures.

2.1.1 Dataset 1: Younger adult study

2.1.1.1 Participants

These data originated in a pharmacological challenge study investigating the acute and persisting effects of racemic ketamine (Murphy *et al.*, 2020). Participants were recruited either via public announcements or from an existing database of participants who took part in previous studies of the *Clinical Affective Neuroimaging Laboratory* (CANLAB) & Leibniz Institute for Neurobiology, Magdeburg, Germany. Right-handed male participants aged 18-55 years were included in the study. Exclusion criteria were a current or lifetime major psychiatric disorder, including substance or alcohol dependence or abuse, according to DSM-IV; family history of psychiatric disorders as assessed by a demographic questionnaire; and neurological or physical constraints or severe illnesses as evaluated by a study physician during screening. The clinical laboratory tests used to evaluate the participants health included a thyroid function and a liver function tests, an electrocardiogram, a complete blood count, and an electrolyte test. Only males were recruited in this study to reduce variability in the sample. Further exclusion criteria were technological barriers to completing the assessment at home (e.g., lack of Wi-Fi connection) and colour-blindness. Participants were compensated with €500 (~US$625), which participants received after their

involvement in the study, but that amount was not pro-rated to session-wise adherence. This study was approved by the Institutional Review Board of the Otto-von-Guericke University Magdeburg, Germany, and informed consent was obtained from all participants. Participants' data were collected, processed, and shared between sites according to the European General Data Protection Regulation (GDPR) and any applicable national privacy regulation.

2.1.1.2 Procedure

This study was a placebo-controlled, double-blind, randomized, cross-over study designed to investigate the acute and persistent effects of ketamine on EEG and behavioural measures. Participants were invited to the laboratory on five different occasions to complete repeated measurements: at enrolment/screening (visit 1); on the days of infusion of ketamine or saline placebo (visits 2 and 4); and on the days after infusion (visits 3 and 5). The two infusion days took place four weeks apart following the same study protocol, while timing of ketamine or saline administration was counter-balanced. Throughout the study, additional task-driven EEG data collection was remotely performed by participants unsupervised in the home, for a week period prior to and after each infusion session (four weeks in total).

2.1.1.2.1 Enrolment session in-laboratory

The enrolment session, including screening examination, was performed between 21 and 7 days prior to the first infusion session for each participant. After having the purpose and risks of the study explained, all subjects signed an informed consent form, provided a detailed medical history, and completed screening. It included physical, neurological, and psychiatric examinations, a 12-lead ECG recording, and blood draws for clinical laboratory (including serology), as outlined in the section on inclusion/exclusion above. Then, three research assistants and I trained participants in the use of the Cumulus Neuroscience platform and completed the full suite of at-home tasks as well as two additional standard laboratory tasks while their brain activity was being recorded, all under supervision of a researcher. At the end of the session, they were given the EEG cap and tablet

to take home to carry out their at-home sessions unsupervised. This first session lasted between 3.5 to 4 hrs.

2.1.1.2.2 At-home phase

Participants were instructed to perform daily recordings during the week before and after each infusion session, for a total duration of 4 weeks. Each recording session (including set-up and calibration for signal quality) lasted approximately 45 mins. Participants were instructed to complete their sessions in a quiet place at home around a regular time of the day between 5 and 9 pm, when they would not be disturbed.

The at-home task list included: Sonic Scenes (app-based MMN task), Astrotap (gamified visual Oddball task), Go With The Flow (gamified Flanker task) and a resting state recording with eyes open and closed. A lifestyle questionnaire was also used to collect relevant daily variables such as mood, sleep quality, caffeine and alcohol intake. Adherence to the study protocol was remotely monitored through the Cumulus web dashboard.

2.1.1.2.3 Infusion days in-laboratory

Participants visited the laboratory on two separate occasions to undergo either the ketamine or saline infusion protocol. Before each infusion, participants completed a set of questionnaires including the Clinician administered Dissociative States Scale (CADSS), Montgomery Asberg Depression Scale (MADRS), and the Snaith-Hamilton-Pleasure-Scale (SHAPS) (Montgomery and Asberg, 1979; Snaith *et al.*, 1995; Bremner *et al.*, 1998). Same-day in-laboratory baseline EEG recording was also collected immediately before the infusion under the supervision of the research team. Headset setup was carried out by the participant as in the home, but with an extra manual check of signal quality by research staff. The infusion day task list included the at-home task list followed by a conventional laboratory-style Flanker task and a conventional Stop-Signal task. Then, the participants were administered a single IV infusion (of a total volume of 50 ml) of 0.5 mg/Kg of racemic ketamine hydrochloride, over 40 mins, or IV saline solution over 40 mins.

During the infusion, participants were seated in a comfortable chair and their legs were elevated on a footrest. Their overall mobility was restricted as a cannula was placed in each of their arms. One cannula was used for delivering the ketamine or saline infusion and the other one to collect blood draws. Only for this phase of the recordings, the tablet was mounted on a tablet holder and operated by the researchers as participants were not able to bend their arms at that time. Eyes-closed resting state EEG recordings were collected during the first 20 mins of the infusion. Then, after a short break the MMN task was administrated during the remaining 15 mins of the infusion (see Figure 7 for the infusion protocol diagram.).

The infusion was followed by a 20-min break during which the study doctor checked in with the participants and ensure that their vital signs were within safe bounds. After that, they repeated the same expanded task list as was used directly before infusion. Finally, after a second break of 30 mins during which they received a snack and a visit from the study doctor, the participants filled in the same series of questionnaires as before the infusion (CADSS, MADRS, SHAPS) as well as the 5D-ABZ to measure altered state of consciousness (Dittrich, Lamparter and Maurer, 2006), and performed a neurofeedback task (not described in this thesis). Blood samples were collected before during and after the infusion. Blood pressure was collected every half hour up until 3 hrs after the infusion.

2.1.1.2.4 Post-Infusion days in-laboratory

Participants came to the laboratory to perform the expanded infusion day task list a third time, approximatively 24 hrs after their infusion. They also completed the state questionnaires once again (CADSS, MADRS, SHAPS) and provided a blood sample.

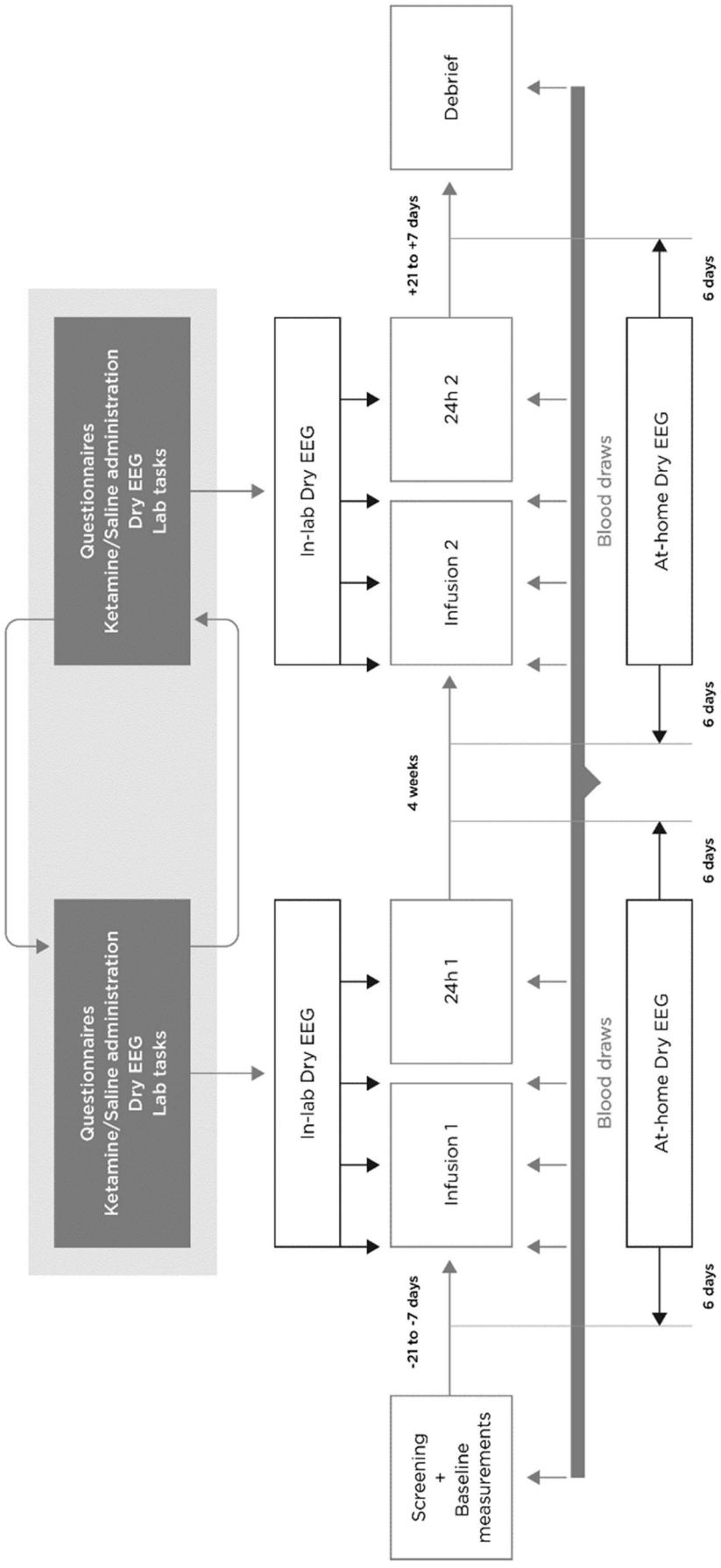


Figure 6: Diagram of the younger adult study design

Figure 7: Infusion Day protocol

2.1.2 Dataset 2: Older adult study

2.1.2.1 Participants

This dataset was collected within the context of a larger study on memory performance in healthy aging. Participants were drawn either from an existing database of older adults who had previously taken part in research studies at Trinity College Dublin, Ireland, or recruited directly from the local community via word-of-mouth, newspapers, posters, and Facebook advertisements. Participants were included if they were >55 years old. Exclusion criteria were a current diagnosis of, or taking medications for, any psychiatric or neurological illness; substance abuse; colour-blindness; or technological barriers to completing the assessment at home (e.g., lack of Wi-Fi connection). Participants also completed the Wechsler Memory Scale Logical Memory test (WMS-IV) (Chelune, Bornstein and Prifitera, 1990), the National Adult Reading Test (NART; a measure of pre-morbid IQ) (Bright, Jaldow and Kopelman, 2002) and the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005). Participation in the dry EEG portion of the study was contingent on a MoCA score >23 (per Murphy et al. 2019). All participants were compensated with €20 (~US$25) at the end of the screening session. If they agreed to participate in the at-home part of the study, they received an additional €40 for their participation, which was not contingent on adherence. The study was approved by the ethics committee of the School of Psychology of Trinity College Dublin, Ireland, and informed consent was obtained from all participants. Participants' data were collected, processed, and shared between sites according to the European General Data Protection Regulation (GDPR) and any applicable national privacy regulation.

2.1.2.2 Procedure

Participants were asked to complete a suite of gamified tasks 5 days per week for 6 weeks: visual Oddball, Flanker, N-back, and delayed match-to-sample tasks, plus resting state, during simultaneous dry EEG recordings, unsupervised in the home using the dry EEG recording platform.

Due to the cumulative length of the tasks, they were split across two alternating daily protocols, meaning that the Oddball and Flanker games were scheduled on every second day of participation.

2.1.2.2.1 Enrolment session in-laboratory

Participants were invited to the laboratory to be trained on the dry EEG platform use. Upon arrival, they provided informed consent and were fitted to the correct headset size. Participants then completed a training session on how to use the headset and tablet. This training was led by a research assistant and explained how to: log into the application; put on the headset following the in-built, step-by-step instructions of the mobile app delivering the task suite; and a practice run of each game until they felt confident playing the game. After training, all tasks were performed under dry EEG. Participants were then given the EEG headset and tablet to perform the at-home recordings. This initial session lasted approximately 2 hrs, with dry EEG onboarding, familiarization and initial recordings with these two tasks took approximately 1 hr. Participants were the sole recipient of the training on how to use the platform (i.e., no study partners or carers were involved in the study nor participated in this onboarding session).

2.1.2.2.2 At-home phase

Each daily session comprised a resting state recording with eyes open and closed (1 min each) and two of the four games (alternating between sessions). Participants were instructed to complete their EEG sessions in a quiet place at home at any time that would suit them, when they would not be disturbed. Sessions carried in the home lasted <30 mins. The gamified Oddball, Flanker and delayed match-to-sample tasks lasted about 12, 7 and 10 mins, respectively. Resting state recordings lasted ~2 mins, the N-back tasks ~ 5 mins. Only data extracted from the gamified Flanker and Oddball tasks are presented here. The order of the gamified tasks was randomized on each day to mitigate order and fatigue effects.

2.2 The Cumulus platform

2.2.1 The Cumulus Dry EEG headset

The Cumulus dry EEG headset consists of a wireless 16-channel dry sensor EEG headset (Cumulus; www.cumulusneuro.com). Flexible Ag/AgCl coated polymer sensors of a comb-design (ANT-Neuro/eemagine GmbH) are used to achieve a stable and dermatologically safe contact to the scalp at 16 channels (10:10 locations: O1, O2, P3, Pz, P4, Cz, FT7, FC3, FCz, FC4, FT8, Fz, AF7, AF8, FPz; Figure 9). The left mastoid is used for reference and the right mastoid for driven-bias, with single-use, snap-on electrodes attached to wires extending from the headset (Figure 8). The mastoids sensors consist of gel-based single-use disposable Kendall™ electrodes. The headset has an input impedance of 1 GΩ with features including common-mode rejection, and built-in impedance checking. The electronics and sensors are mounted on a flexible neoprene net for comfort and the stretchable structure was designed to enable consistent placement by non-experts in line with the 10-10 sensor system. An onboard processor and Bluetooth module transmitted 250 Hz EEG data to an Android tablet, from where it is transferred to a secure cloud server for storage and processing.

Wireless Specification	Bluetooth	Bluetooth 4.1
	Bandwidth	>1Mbps download
	Security	WPA2 or WPA3 recommended
EEG data acquisition	Sampling frequency	250Hz
	Dynamic range (resolution)	24 bits
	Measurement noise	1 µV
	Input impedance	1000MΩ
	Common Mode Rejection Ratio (theoretical)	110dB
	Common Mode Rejection Ratio (measured)	80dB
Others	Battery life (normal operating mode)	6 hrs
	Sensors	16 channel, dry sensors, coated Ag/AgCL on Polyurethane (PU)
	Headset weight	260g
	Analog-to-Digital Converter	ADS1299 chip from Texas Instruments

Table 1: Technical specifications of the Cumulus dry EEG recording headset.

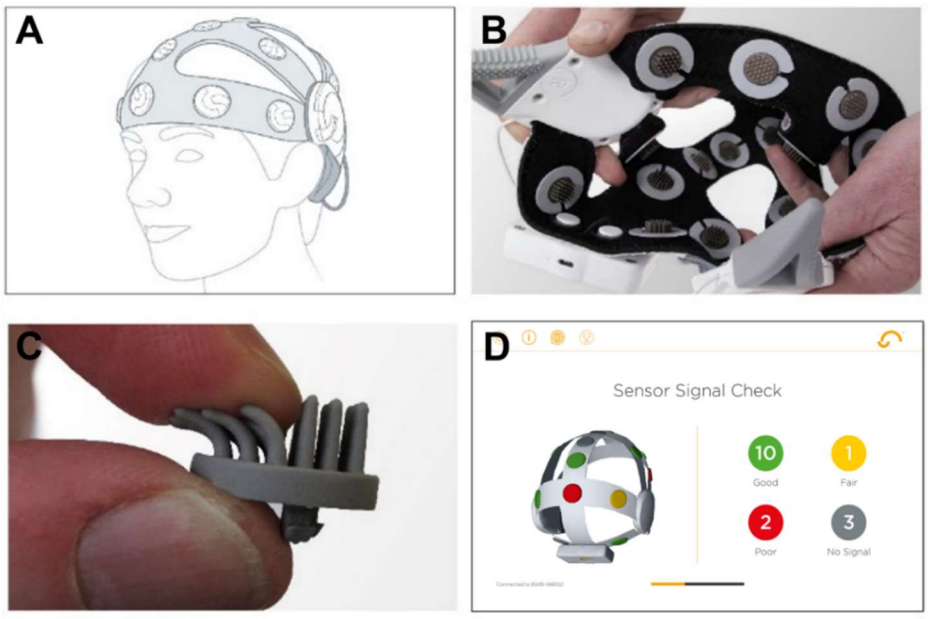


Figure 8: Cumulus dry EEG recording headset. A: Positioning of the headset on the head, B: Interior of the dry EEG cap, C: Dry EEG electrode, D: Screenshot of the built-in calibration step in the mobile app.

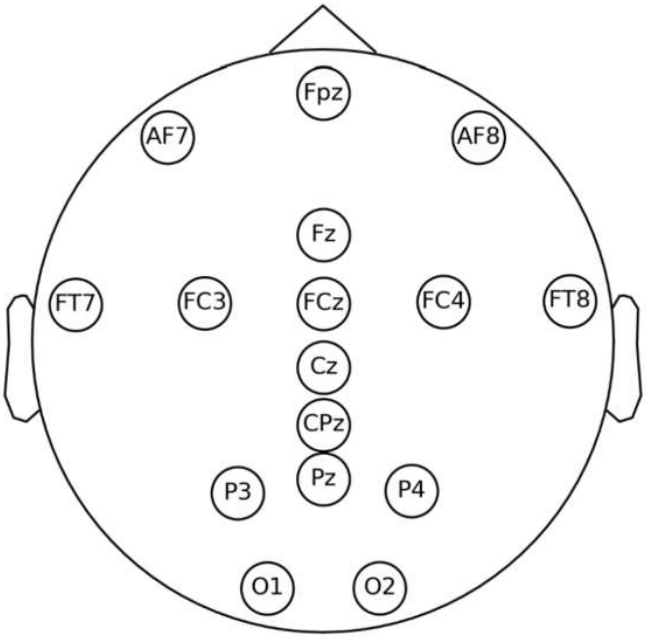


Figure 9: Cumulus dry EEG recording headset scheme. The Cumulus headset has 16 channels at standard 10-20 positions. Electrode labels encode the brain region (Anterior, Frontal, Temporal, Central, Parietal, Occipital) and hemisphere (odd numbers to the left, even to the right).

2.2.2 Mobile App interface

Upon logging into the app, a stepwise tutorial guides participants through the headset configuration (head placement, positioning of detachable mastoid sensors and feedback on electrode impedances) in preparation for recording data during the gamified tasks. Cloud-based secure methods are used for collection and automatic processing of behavioural and EEG data, as well as integration with other data streams (in the presented studies participants wore a fitness tracker, the Withings Go, https://www.withings.com/) and web-based dashboards for monitoring and data visualization on a daily, session-by-session basis.

2.2.3 Resting State and Cognitive Task Paradigms

The gamified tasks are proprietary to the technology provider, and not all details of task mechanisms are in the public domain. Core information about the task structure is provided here, as it relates to the user experience of performing the tasks.

2.2.3.1 Resting state recordings

2.2.3.1.1 Resting state recordings in the Younger adult study

During the infusion sessions, resting state EEG recordings were collected during the first 20 mins of the infusion, while participants were asked to hold their eyes closed. For all other sessions, in-laboratory and at-home, resting state recordings were collected at the beginning of each session, lasting 7 mins in total. During the first minute of recordings, participants were asked to complete a Berger-procedure which consisted in closing and opening their eyes every 10 seconds for a minute. It was then followed by one minute of eyes open recording and 5 mins eyes closed.

2.2.3.1.2 Resting state recordings in the Older adult study

Resting state recordings were collected at the beginning of each session just after the completion of the lifestyle questionnaire. It lasted 2 mins in total. During the first minute of recordings, participants were asked to keep their eyes open. It was then followed by one minute of eyes closed recording.

2.2.3.2 Gamified visual Oddball Task

Within each session, target and non-target stimuli are randomly presented across five levels (blocks) of gameplay. In the older adult cohort, targets and non-targets were 'aliens' of different colours, expressions, and hairstyles. Responses were made by tapping directly on the stimuli on the tablet screen. In the younger adult cohort (data collected 6 months after the first cohort), the game had been modified in two specific ways: i) non-target stimuli were 'astronauts', not aliens; and ii) responses were captured by tapping on buttons located on either side of the screen. Participants could use either button, and each button operated the same way. This was implemented to accommodate both right- and left-handed people. In both studies, the target aliens changed between levels for variety in gameplay and to encourage an attentive player strategy. One complete game session corresponded to the presentation of 30 Target stimuli requiring a behavioural response, 70 Non-Target stimuli, which should be ignored, and 5 'bonus' targets which have a consistent appearance throughout the game (yellow stars). During gameplay, the upcoming stimulus locations were highlighted prior to stimulus presentation to encourage user attention, in a manner functionally similar to a fixation cross. Stimuli (e.g., aliens, astronauts) were then visible on-screen for 200ms. Points were awarded for a correct response and deducted for an incorrect response, in conjunction with auditory feedback. Points awarded for correct responses were mapped to reaction time (faster responses gained more points) to encourage attention and faster response. Each gameplay session lasted approximately 12 mins. Screenshots of the gamified Oddball task are presented in Figure 10. Task graphics were designed with a colour-blind-safe palette. In this report, two ERP conditions are evaluated and will be referred as 'Target' and 'Non-Target' hereafter. The Target condition corresponds to trials in which the presentation of a Target stimulus was correctly responded to. The Non-Target condition corresponds to trials in which participants correctly refrained from tapping a Non-Target stimulus. Any trials where participants responded incorrectly are excluded from analysis.

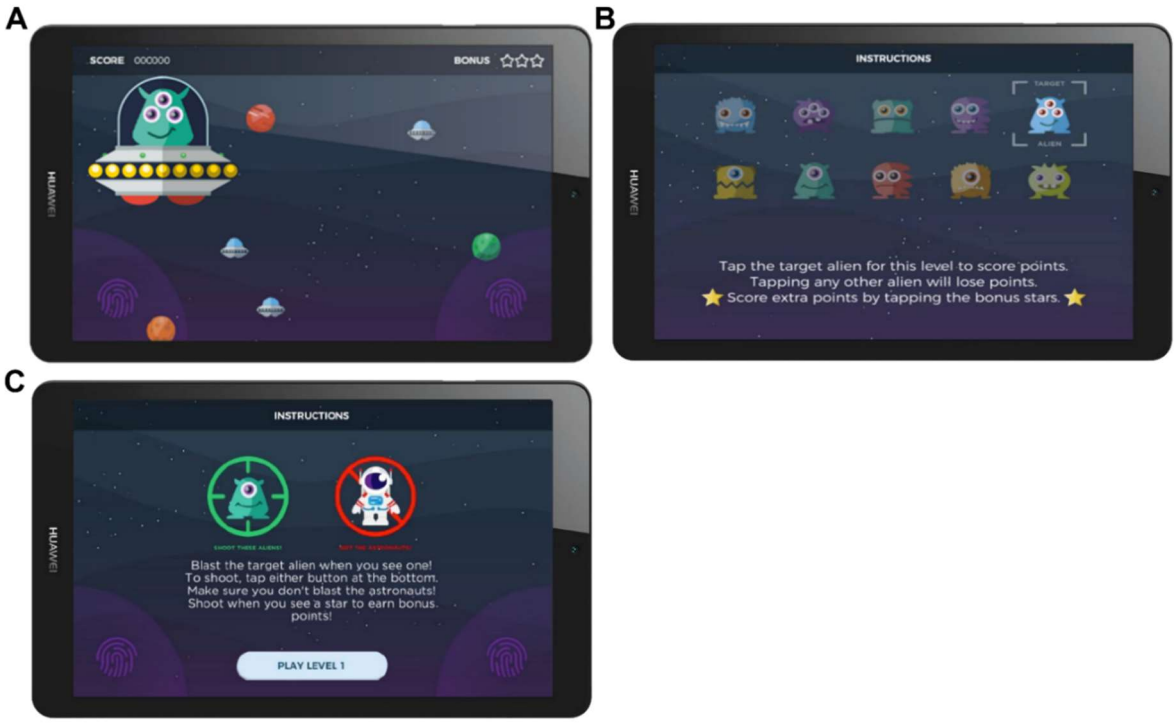


Figure 10: Screenshots of the gamified Oddball task. A: Screenshots of the stimulus presentation, B: Instruction screen in the Older Adult Study, C: Instruction screen in the Younger Adult Study.

2.2.3.3 Gamified Adaptive Flanker task

At the beginning of each trial, flanking stimuli – a shoal of orange fish – appeared first on screen, pointing either leftward or rightward, followed 200ms later by the target (an identical orange fish of the same size) positioned in the centre of the array. Participants responded by tapping either the left or right side of the screen, matching the direction in which the central target stimulus was pointing. The flanking stimuli pointed either in the same direction as the target (a 'congruent' trial), or the opposite direction (an 'incongruent' trial). The background colour changed between levels for variety in gameplay. Participants were encouraged not to exclusively prioritize accuracy over speed in two ways: the response time window was shortened with correct responses and lengthened with incorrect responses, and higher points were awarded for quicker responses. These constraints and incentives were designed such that the ideal strategy for maximum points was to respond as quickly as possible and thereby make some mistakes. Gameplay adjustment values were calibrated to produce sufficient numbers of incorrect responses per session (typically

between 10-20%) to enable ERP averaging. The task consisted of 150 trials divided into 5 blocks of 30 trials each, evenly split between congruent and incongruent trials. Each session lasts approximately 7 mins. Screenshots of the gamified Flanker task are presented in Figure 11. Task graphics were designed with a colour-blind-safe palette.

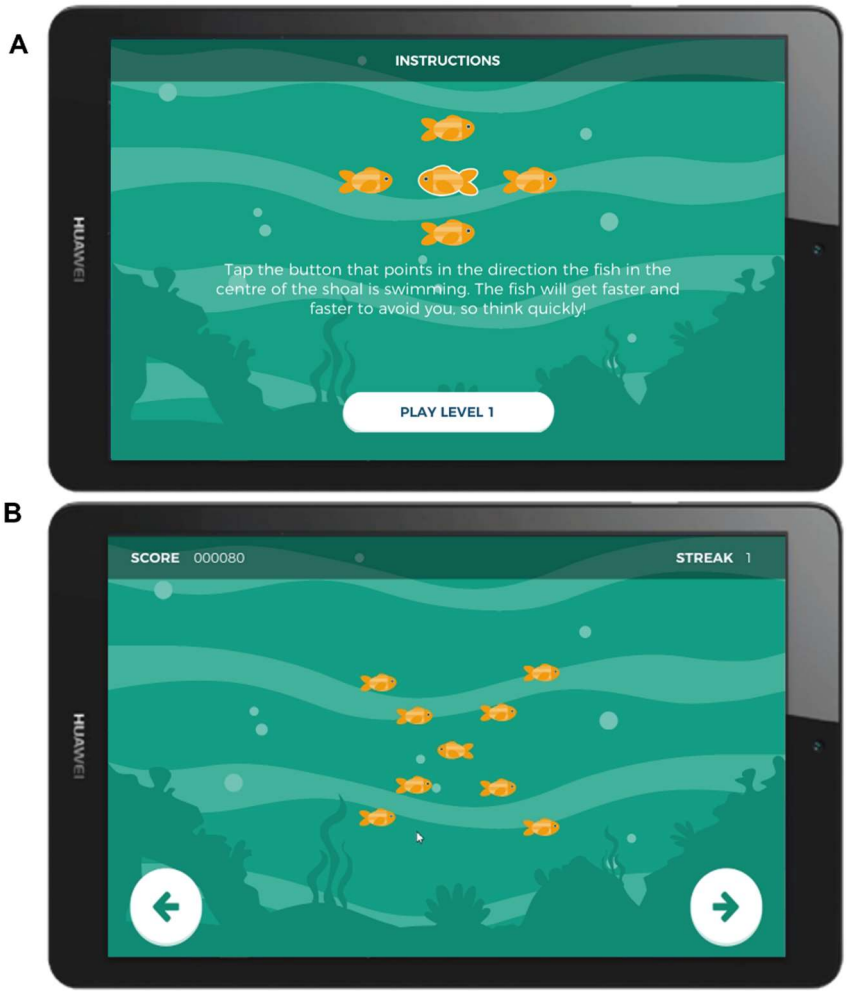


Figure 11: Screenshots of Gamified Adaptive Flanker task. A] Instruction screen, B] Screenshots of the stimulus presentation.

2.2.3.4 App-based Passive Auditory Oddball

Sonic Scenes is an integrated MMN-silent video paradigm. The participant is prompted to put on headphones and adjust the volume until he can clearly hear some sample tones. When ready, the

participant presses play on a silent movie, which lasts 15 mins. Tones play throughout, while the participant watches the film. Eight short films are used in an arbitrary cycled order, each consisting of silent clip montages compiled from stock footage. There were no narrative nor subtitles. Each movie session incorporates 1000 ‘standard’ tones (100ms; 1000Hz) and 200 pitch deviants (100ms; 1200Hz).

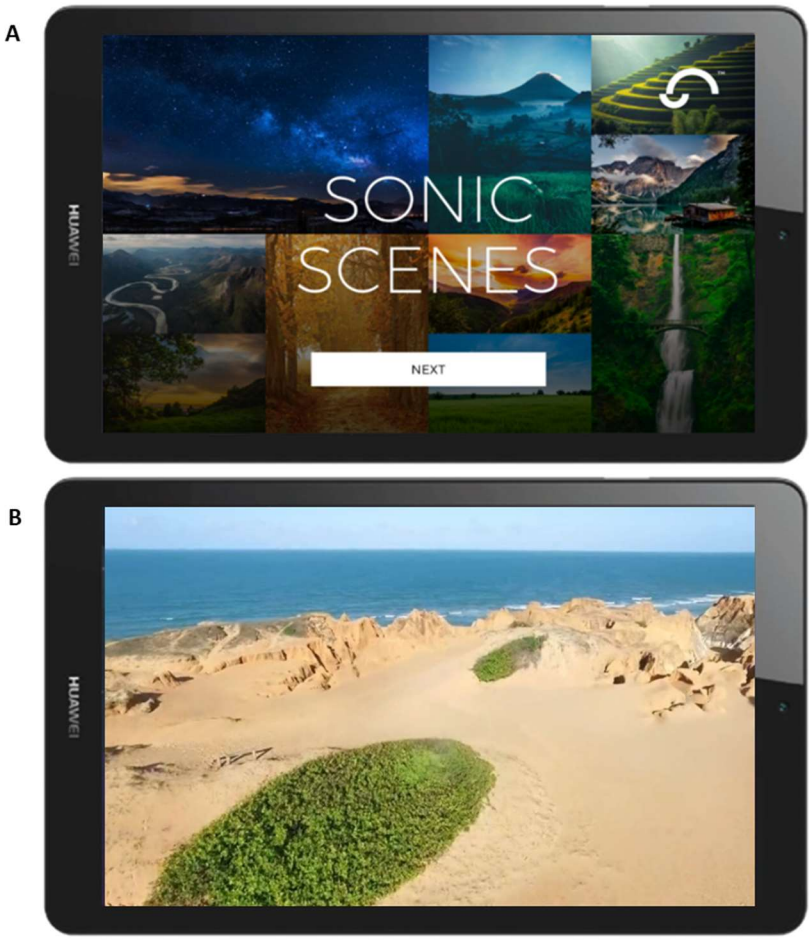


Figure 12: Screenshots of Gamified Mismatch Negativity task. A] Home screen, B] Screenshots of the silent movie.

2.2.4 Dry EEG preprocessing

At the end of each session, the EEG data is automatically uploaded to the cloud and the proprietary processing pipeline developed by the technology provider is applied. The Cumulus processing suite is proprietary to the technology provider, and not all details of the data cleaning procedure are in the public domain. This was designed to verify and correct the integrity of timing information and exclude bad quality signal portions. Corrective procedures are applied for missing and anomalous data, including eye and other characteristic artefacts. After that, EEG signals is pre-processed with filtering from 0.25 – 40 Hz, epoch extraction, and baseline adjustment. All data are recorded with a left-mastoid reference. Oddball task epochs are extracted from 500ms before target stimulus presentation to 1000ms after. ERP epochs are baseline adjusted at each electrode by subtracting the mean signal in the 200ms time window preceding stimulus presentation. Epochs from the Flanker task are extracted from 500ms before participant's responses to 1000ms after. ERP epochs were baseline adjusted at each electrode by subtracting the mean signal in the 200ms time window from 400 to 200ms before a participant's response. Epochs from the MMN task which were extracted from 200ms before stimulus presentation to 600ms after. ERP epochs are baseline adjusted at each electrode by subtracting the mean signal in the 200ms time window preceding stimulus presentation.

After the application of the Cumulus pipeline, as an additional step to improve data quality, noisy epochs are then identified and removed. Epochs are selected per channel following a stepwise procedure. First, epochs with an absolute voltage >100µV are rejected. In each remaining epoch, ERP amplitude is correlated with the session average (the data were ERP amplitudes at each timepoint). Any epoch with a correlation to the session average of less than 0.25 is rejected. This threshold was selected to allow for variability in the retained data while rejecting trials that diverged the most from the session average. Following this, a z-score-based data-cleaning approach is used to further remove outliers. To do this, a set of temporal and spectral metrics are calculated and z-scores for each metric are obtained. These temporal and spectral metrics consists

of the Hurst exponent, kurtosis, median gradient value, range, variance, standard deviation, and ratio of high frequency to low frequency power. These metrics are commonly used in EEG data selection steps (Nolan, Whelan and Reilly, 2010). First, all epochs with z-scores >15 in any metric were rejected. Next, any epochs with a Hurst exponent <0.65 or the spectral peak <0.1, respectively, were rejected. Finally, any remaining epochs with z-score >4 in any metric were rejected. Median ERP amplitudes were then calculated as it is a robust measure of central tendency.

3 Empirical Chapter 1

Feasibility and variability of gamified remote EEG

3.1 Introduction

Reliable, objective assessment of brain function is a crucial part of the evidence base for cognitive neuroscience and for the characterization of neurodegenerative, neurodevelopmental, and neuropsychiatric disorders. Many external factors can affect measurements of cognitive functioning, including mood, stress, and energy levels (Dustman *et al.*, 1990; Barry *et al.*, 2005; De Kloet, Joëls and Holsboer, 2005; Brose *et al.*, 2012; Shochat, 2012; Brose, Lövdén and Schmiedek, 2014; Fleck *et al.*, 2019; Wilks *et al.*, 2021). As such, measuring brain activity at any single time point may not accurately reflect a person's typical neurocognitive profile. Furthermore, individual and group-level estimates of neurophysiological phenomena may improve with aggregation over larger samples – the same principle that underlies the use of repeated samples in a single behavioural or neuroimaging experimental session. Repeated recording of brain activity – over many days – may therefore allow for the identification of more reliable metrics of brain function and cognitive performance, that account for day-to-day variability (Kam *et al.*, 2019; Lau-Zhu, Lau and McLoughlin, 2019; Hinrichs *et al.*, 2020).

To date, evaluation of dry EEG has consisted of direct comparisons with conventional wet (i.e., electrolytic gel or water-based) technology or test-retest assessments in controlled environments (Hairston *et al.*, 2014; Barham *et al.*, 2017; Krigolson *et al.*, 2017; Mathewson, Harrison and Kizuk, 2017; Radüntz, 2018; Kam *et al.*, 2019; Hinrichs *et al.*, 2020). While these studies demonstrated that dry EEG can perform similarly to wet EEG in controlled settings, they did not address the question of EEG feasibility and variability in ecologically valid environments. In particular, the usability of self-administered EEG as well as the amount of data (i.e. trials, sessions) required from at-home settings when data is self-recorded is unclear. Previous work demonstrated the face validity of gamified visual Oddball and Flanker EEG tasks (McWilliams *et al.*, 2021). McWilliams and colleagues demonstrated that ERPs evoked from gamified tasks yield signals similar in morphology and topography to those evoked by standard neurocognitive tasks used in EEG

research. Here I aim to further that validation by looking at the variability of signals over repeated at-home sessions.

A key question when designing ERP studies is the strategy taken to balance the quality and quantity of data recorded, as this will have an effect on the statistical power of experimental analyses. In laboratory environments it is straightforward to control signal quality, but noise and artefacts still occur, meaning choices must be made in how participants and/or individual behavioural trials (and the EEG epochs they correspond to) are included or excluded – which may be more liberal (lower quality, higher quantity) or conservative (higher quality, lower quantity). The desire to record more trials, over a longer task duration, must be balanced against considerations of a fair burden on users, and the fact that participants may become fatigued and/or disengaged over time. In a remote study, self-administered by non-experts, there are additional challenges to quality (which we may expect to be more variable than in controlled laboratory settings), but opportunities for data quantity, as it is feasible to ask participants to split a larger amount of task-driven behavioural interaction over a number of days. In this chapter, I explore this question in the context of gamified tasks that should encourage repeated task engagement, and with older and younger user groups for which usability and familiarity with technology may be an issue.

Here, I conducted post-hoc analyses of two pre-existing datasets collected for other purposes. Longitudinal dry EEG data were collected from two separate cohorts: older adults aged 55+ years over 6 weeks (Murphy *et al.*, 2019), and younger adults aged 18-35 over 4 weeks (Murphy *et al.*, 2020). In the younger adult study, a pharmacological challenge with ketamine was used in a cross-over design, but the EEG data reported in this chapter was from the non-ketamine control condition only. Participants were asked to complete gamified Oddball and Flanker tasks 5-7 times per week while EEG was simultaneously recorded. I sought to evaluate if dry EEG recorded in the home by unsupervised participants over multiple sessions could yield datasets of the same aggregate quality as published results derived from a single wet EEG session recorded in a

controlled environment. I evaluated dry EEG signal quality and usability by cohort (older vs. younger adults) and by gamified task (Oddball vs. Flanker). I expected that, when comparing equal numbers of trials, the signal quality of dry EEG would be lower than that of wet EEG; however, I predicted that similar signal quality could be achieved by aggregating dry EEG data across multiple sessions from each participant. To the best of my knowledge, no published study has quantified the variability of self-administered EEG recorded remotely in younger and older population via gamified neurocognitive tasks.

3.2 Methods

3.2.1 Dry EEG Datasets

The two dry EEG datasets evaluated in this chapter are described in section 2.1 of this thesis. As the focus of this chapter was to evaluate usability and fidelity of dry EEG recording, data analysis of the younger adult dataset is limited to the EEG data collected prior to the ketamine administration intervention are evaluated. Pharmacological effects are not described here. In contrast, the adherence report encompasses all sessions collected during the entire study. The acute and persistent effects of ketamine on brain activity and cognitive functions are discussed in Empirical Chapter 2 of this thesis.

3.2.2 Behavioural data analyses

Only behavioural data corresponding to correct trials are presented in this analysis. For the Oddball task, 'correct trials' refers to correct target identification. For the Flanker task, it corresponded to trials on which the target stimulus direction was correctly identified. To investigate the impact of practice effects on reaction time (RT), we computed participants' mean RT across their first 7 sessions. This time window was selected so to avoid any confounding drug effects in the Younger Adult Study. For the Older Adult Study, only participants that completed at least 7 sessions of each task were included in these analyses. For the Younger Adult Study, only participants that completed at least 7 sessions of each task before the first infusion session were

included in the analyses. Linear mixed-effects (LME) models were used to investigate the effect of sessions on RTs. In these models, participants were random intercepts and sessions were fixed effects. This analysis was conducted using the Statsmodels package (version 0.10.1; https://www.statsmodels.org/devel/mixed_linear.html, RRID:SCR_016074) in Python (version 3.6.9, RRID:SCR_008394). Normality of the residuals distribution was assessed by visual inspection.

3.2.3 Usability analyses

To quantify the platform usability, I recorded if participants used the hardware correctly when unsupervised, and I measured subjective feedback via a usability questionnaire. To assess how often participants were using the recording platform, mean number of at-home sessions completed per week and total mean numbers of sessions per participant were computed. To assess participants' ability to use the recording platform unsupervised, I computed the percentage of sessions that had successfully been conducted in the home. Success was defined as complete EEG and behavioural log files containing all the tasks of the day. I report the mean percentage of successful sessions per participant. Participants' subjective feedback on the technology was captured via the *System Usability Scale*, a 10-item industry standard questionnaire (J. Brooke, 1996) designed specifically to develop and assess the use of technology in industry. The System Usability Scale (SUS) is one of the most widely cited and used User Experience Scales (UX) and considered to be a highly robust and versatile tool (Bangor, Kortum and Miller, 2008; Lewis, 2018b, 2018a). It was chosen as it is an easy and quick validated test to evaluate usability that is widely for various types of systems including mobile apps (Beul-Leusmann *et al.*, 2014; Hussain *et al.*, 2017; Adinda and Suzianti, 2018), websites (H.N, Nugroho and Ferdiana, 2015), serious games (Tolentino *et al.*, 2011), etc. It has also been used internationally and is translated into many languages including French (Gronier and Baudet, 2021), Arabic (AlGhannam *et al.*, 2018), Polish (Borkowska and Jach, 2017), Greek (Katsanos, Tselios and Xenos, 2012), American sign language (Berke, Huenerfauth and Patel, 2019). In both studies, the completion of the SUS questionnaire

was optional and performed at the end of the study after the participants returned their hardware. It was administrated by the researchers either over the phone when participants mailed back their equipment, or in-person when participants dropped by the laboratories to return their headset and tablet. SUS scores from the younger and older adults were compared using one-sided non-parametric Mann-Whitney U rank test to evaluate whether age could modulate usability.

3.2.4 EEG Analyses

Analyses conducted on the Younger Adult Study dataset only included data collected during the week before the pharmacological interventions to avoid any confounding effects. The preprocessing approach used on the dry EEG data is described in section 2.2.4 of this thesis.

3.2.4.1 EEG data collection success rate computation

Dry EEG signal quality depends greatly on the specific hardware and how it is used. To check the amount of usable data that was kept after the preprocessing and trial selection steps described in section 2.2.4, I calculated success rates of data collection. I report the mean number of trials available per participants for each task and condition. The number of sessions surviving after the preprocessing and trial selection steps (as all trials in a session could be rejected) were used to calculate the success rates, as a percentage of the total number of sessions recorded. For each task, the percentage of successful sessions was computed for all participants in both studies.

3.2.4.2 EEG signal variability quantification

3.2.4.2.1 At-home data variability

To evaluate signal quality as a function of the number of trials available, I computed the Standardized Measurement Error, SME_i , for each participant *i* and for various number of trials according to the following equation (Clayson, Brush and Hajcak, 2021; Luck *et al.*, 2021):

$$SME_i = \frac{\sigma_i}{\sqrt{n_i}} \qquad \text{(Eq. 1)}$$

where σ_i corresponds to the standard deviation of the metric of interest, and n_i, to the number of trials available. Luck and colleagues define the SME as *"the standard error of measurement for an ERP amplitude or latency score."*. To keep our analyses centred on data quality and avoid having to account for the variability introduced by different peak selection approaches, I focused on the time-window mean amplitude approach (Luck *et al.*, 2021). ERP amplitudes extracted from the Oddball task were calculated by taking the mean voltage amplitude across the 300-600 windows after stimulus presentation. Analyses of the Oddball and Flanker tasks were focused on electrodes Pz and FCz, respectively. These electrodes were chosen as the P300 and ERN signals are expected to be maximal around central and fronto-central regions, respectively (Kappenman *et al.*, 2021). ERP amplitudes extracted from the Flanker task were calculated by taking the mean voltage amplitude between 0-100ms time windows after participants' response for both Correct and Incorrect trials. The standard deviation of these time-window mean scores σ_i was then used to compute the SME_i. The trials used for the calculation were added in sequential order, meaning that trials were aggregated as they were recorded: when calculating the SME for *n* trials, the first *n* available trials of a participant were used.

I report group-level SME for increasing numbers of at-home trials, aggregated over multiple sessions. The corresponding 95% confidence intervals were computed as the standard error of the SME across all participants, divided by the square root of *N,* the number of participants. I note that as I increased the number of trials to aggregate, fewer participants had sufficient data to be included and I quantify this in each analysis. SME is compared to the value achieved in the wet EEG reference dataset, and the number of trials in wet and dry studies, after their respective trial rejection procedure.

Finally, I tried to answer the question of how much at-home gamified dry-EEG data is as good or better than a single session's worth of laboratory-derived wet-EEG data. This is not straightforward, as the duration of tasks and rate of trial presentation were not the same in wet and dry settings. However, I did project how many pre-rejection trials of home dry-EEG data would

be required to achieve an SME level similar to laboratory wet-EEG, and therefore how many additional sessions of dry EEG data collection would be required.

3.2.4.2.2 Data quality of dry EEG recordings collected under supervision in the laboratory

To evaluate the impact on data quality of completing the dry EEG recordings in the laboratory in a controlled environment with the supervision of a trained technician, I computed group-level SME for sessions completed in the laboratory for both cohorts. The older cohort only completed one session in the laboratory during their initial on-boarding study visit. For the younger cohort, 3 sessions were completed in the laboratory prior any drug administration: during the initial on-boarding study visit and before the infusion of the ketamine and placebo solutions. I report group-level SME for increasing numbers of in-laboratory trials. The corresponding 95% confidence intervals were computed as the standard error of the SME across all participants, divided by the square root of *N,* the number of participants.

3.2.5 Wet EEG dataset

Wet EEG reference SME values were extracted from the open-source ERP CORE EEG database provided by Luck and colleagues (Kappenman *et al.*, 2021) using Eq.1. The objective of this study was to provide the community with an optimized reference dataset performed by experts in the field of ERP experimentation. Processed and raw data as well as the experiment control scripts can be downloaded at https://doi.org/10.18115/D5JW4R and the details of their Flanker and Oddball tasks have been described in a previous publication (Kappenman *et al.*, 2021). In brief, EEG data was collected from 40 participants (25 females, mean age: 21.5 years old) who completed six 10-minute optimized paradigms including an Oddball and a Flanker task. Although some participants failed to meet the inclusion criteria for some of the components in the original ERP CORE analysis, the data presented here encompasses all 40 participants to represent the entire rate of data quality across participants. In the active visual Oddball task, 4 letters (A, B, C, D, E) were presented in random order and for each block, with one of the letters designated as the Target, and presented with a probability of 0.2. In the Flanker task, a central arrowhead was

the target stimulus and was flanked on each side by a set of arrowheads. These flanking stimuli pointed either in the same direction as the target (a congruent trial) or the opposite direction (an incongruent trial). A Biosemi ActiveTwo recording system with 128 active electrodes (Biosemi B.V., Amsterdam, the Netherlands) was used to collect the data. An average of electrodes P9 and P10 (located near the mastoid) was used to reference the data. Semi-automatic algorithms were used to remove large muscle artifacts, extreme voltage offsets, or break periods longer than two seconds. After that, Independent Component analysis (ICA) was performed, and components associated with eye movements (including eye blinks) were removed. The remaining components were then remixed and projected back to electrode space. These trials were further examined using individualized thresholds and any trial still containing large voltage excursions and large eye movements were excluded. SME values were computed at electrode Pz and across the 300-600 ms time window post stimulus presentation for the Oddball task, and at FCz across the 0-100 ms time-window post participants' response for the Flanker task. SME data, derived from the open-source data, were provided by Prof. Steven Luck's group (personal correspondence 02/04/2022).

ERP Component	Electrode Site	Time-locking Event	Baseline Period	Time-window of analyses
P300 Target	Pz	Stimulus-locked	-200 to 0 ms	300 to 600ms
ERN	FCz	Response-Locked	-400 to -200 ms	0 to 100ms

Table 2: ERPs of interest from the ERP CORE reference wet EEG dataset

3.3 Results

3.3.1 Participants

Of 56 participants recruited in the Older Adult study, 50 commenced and completed the study (see Table 3 for details). Six participants were excluded for the following reasons: two did not meet the inclusion criteria (one was mistakenly enrolled, and another revealed taking medications after enrolment), three were ill during the at-home data collection (unrelated to this study), and one person could not be accommodated due to head size.

In the Younger Adult study, 36 participants were initially recruited but two were excluded for medical reasons and four withdrew. The reasons given for withdrawal were the following: one person expressed discomfort while wearing the headset, one expressed anxiety about the blood draws, one expressed anxiety about taking the drug, and one felt sick during the study (see Table 3).

	Sex	Mean age in years (SD, range)	Mean MoCA Score (SD)	Mean years of Education (SD)
Older Adult study	25 males 25 females	67.84 (5.03,58-81)	27.22 (2.04)	15.24 (3.6)
Younger Adult study	30 males	25.56 (3.74, 18-36)	Not collected	Not collected[a]
Wet EEG study (Kappenman *et al.*, 2021)	25 females 15 males	21.5 (2.87, 18-30)	Not collected	Not collected

Table 3: Participant demographics. SD = standard deviation. [a]83% of the sample were current students.

3.3.2 Usability

In the Younger Adult study, 965 sessions were collected, including 281 sessions collected in the laboratory around the enrolment and infusion sessions. On average, participants attempted 22.87 sessions (SD = 1.92, range: 16-24), of 23 at-home sessions requested (including data from 17 participants who submitted extra sessions). Of 30 participants, 22 attempted the 23 sessions requested. On average, per participant, 96% of the sessions (SD = 5%, range: 79-100%) resulted in a complete EEG/behavioural dataset for input into the preprocessing pipeline. Of 30 participants, 10 successfully completed 100% of their attempted sessions. Weekly adherence results are presented on Figure 13.

In total, 1,499 EEG sessions were collected in the Older Adult study, of which 50 were collected in the laboratory during the enrolment sessions. On average, participants attempted 28.9 at-home sessions (SD = 6.64, range: 10-49), of 29 at-home sessions requested (including sessions from the

24 individuals who submitted more sessions than were requested). Of 50 participants, 33 participants attempted the 29 sessions requested. On average, per participant, 93% of sessions commenced (SD = 7%, range: 73%-100%), resulted in a complete EEG/behavioural dataset for input into the preprocessing pipeline. Of the 50 participants, 12 successfully completed 100% of their attempted sessions.

At conclusion of the studies, 32 of the older participants and 18 of the younger participants chose to complete the optional debrief session, including the self-report SUS usability scale. The mean SUS score at the end of the Older Adult study was 84.53 (SD = 10.15) and 88.33 (SD=10.18) at the end of the Younger Adult study (Figure 14). The individual response components of the scale are displayed in Figure 14. No significant differences were observed between the younger and older cohorts in the main SUS composite score, or any of the individual components (full results are presented in Table 4).

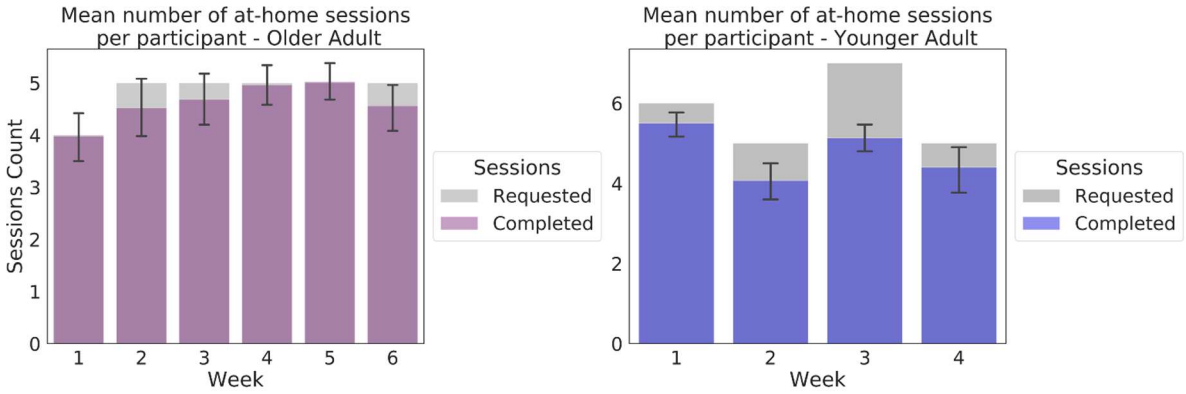


Figure 13: Weekly at-home adherence to the experimental protocol. Data in purple correspond to the Older Adult study (N= 50). Data presented in blue correspond to the Younger Adult study (N=30). Error bars represent 95% confidence intervals. The grey areas correspond to the number of at-home sessions requested in the protocol. The number of sessions requested varied as per protocol, to accommodate scheduled in-laboratory sessions.

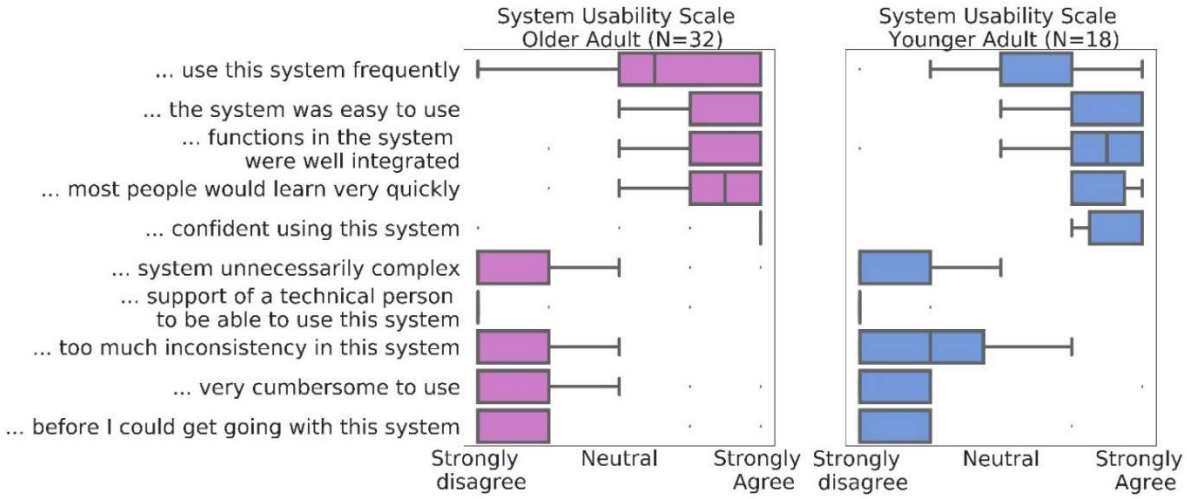


Figure 14: Median System Usability Scale component scores across all participants in the Data of Older Adult study are depicted in purple (N=32), and of the Younger Adult Study in blue (N=18). Whiskers denote interquartile range. Datapoints outside of the 1.5*interquartile ranges were defined as outliers.

	Older Adults (N=32)		Younger Adults (N=18)		
System Usability Scale	***Mean score (SD)***	***Mann–Whitney U statistic***	***Mean score (SD)***	***Mann–Whitney U statistic***	***Uncorrected p-values***
"I think I would like to use this system frequently"	3.47 (1.29)	334.5	3.17 (0.99)	241.5	0.8366
"I found the system unnecessarily complex"	1.69 (1.06)	295.5	1.56 (0.78)	280.5	0.4359
"I thought the system was easy to use"	4.62 (0.61)	323	4.5 (0.62)	253	0.8026
"I think that I would need the support of a technical person to be able to use this system"	1.28 (0.77)	288	1.17 (0.38)	288	0.5063
"I found the various functions in the system were well integrated"	4.53 (0.76)	331.5	4.28 (1.02)	244.5	0.8466
"I thought there was too much inconsistency in this system"	1.34 (0.6)	180.5	1.94 (0.94)	395.5	0.994
"I would imagine that most people would learn very quickly"	4.28 (0.85)	313	4.28 (0.46)	263	0.714
"I found the system very cumbersome to use"	1.59 (1.01)	298.5	1.5 (0.99)	277.5	0.405
"I felt confident using this system"	4.66 (0.83)	300	4.72 (0.46)	276	0.633
"I needed to learn a lot of things before I could get going with this system"	1.84 (1.05)	357.5	1.44 (0.78)	218.5	0.06
Composite Score	84.53 (10.15)	303	83.33 (10.18)	273	0.6235

Table 4: Statistical Analyses of the System Usability Scale. One-sided non-parametric Mann-Whitney U rank test were used to compare the two groups.

3.3.3 Behavioural analyses

In the Older Adult Study, the LME model to analyse RT in the Oddball task contained 343 observations. The LME model to analyse Flanker task RT in all successful trials, and in RT differences in successful incongruent minus congruent trials, contained 336 observations. There was a significant effect of session on RT in the Oddball task, with an average estimated RT decrease of 22.87 ms (SE=1.54, p<10e-49, dfresiduals=341) on each session. There was also a significant effect of sessions on RT in the Flanker task for all successful trials, with an average estimated RT decrease of 17.88 ms (SE=1.01, p<10e-69, dfresiduals=334) on each session. The difference in RT between successful incongruent and congruent flanker trials was also significant, with an average estimated decrease of differences of 3.03 ms (SE=0.52, p<10e-9, dfresiduals=334) between the two RTs with each session. Full results are reported in Table 5 and Figure 15.

In the Younger Adult Study, the LME model analysing Oddball task RT contained 152 observations. There was a significant effect of sessions on RT, with an average estimated RT decrease of 7.24 ms (SE=1.11, p<10e-10, $df_{residuals}$=150) on each session. The LME model analysing Flanker task RT in all successful trials, and differences in RT in successful incongruent minus congruent trials, contained 138 observations. There was a significant effect of sessions on RT with an average estimated RT decrease of 8.87 ms (SE=0.9, p<10e-22, $df_{residuals}$ =136) on each session. The effect of session over the difference in RT across incongruent minus congruent trials was not significant. The decrease of difference between the two RTs by session was estimated at 1.05 ms (SE=0.54, p=0.050, $df_{residuals}$ =136). Full results are reported in Table 5 and Figure 15.

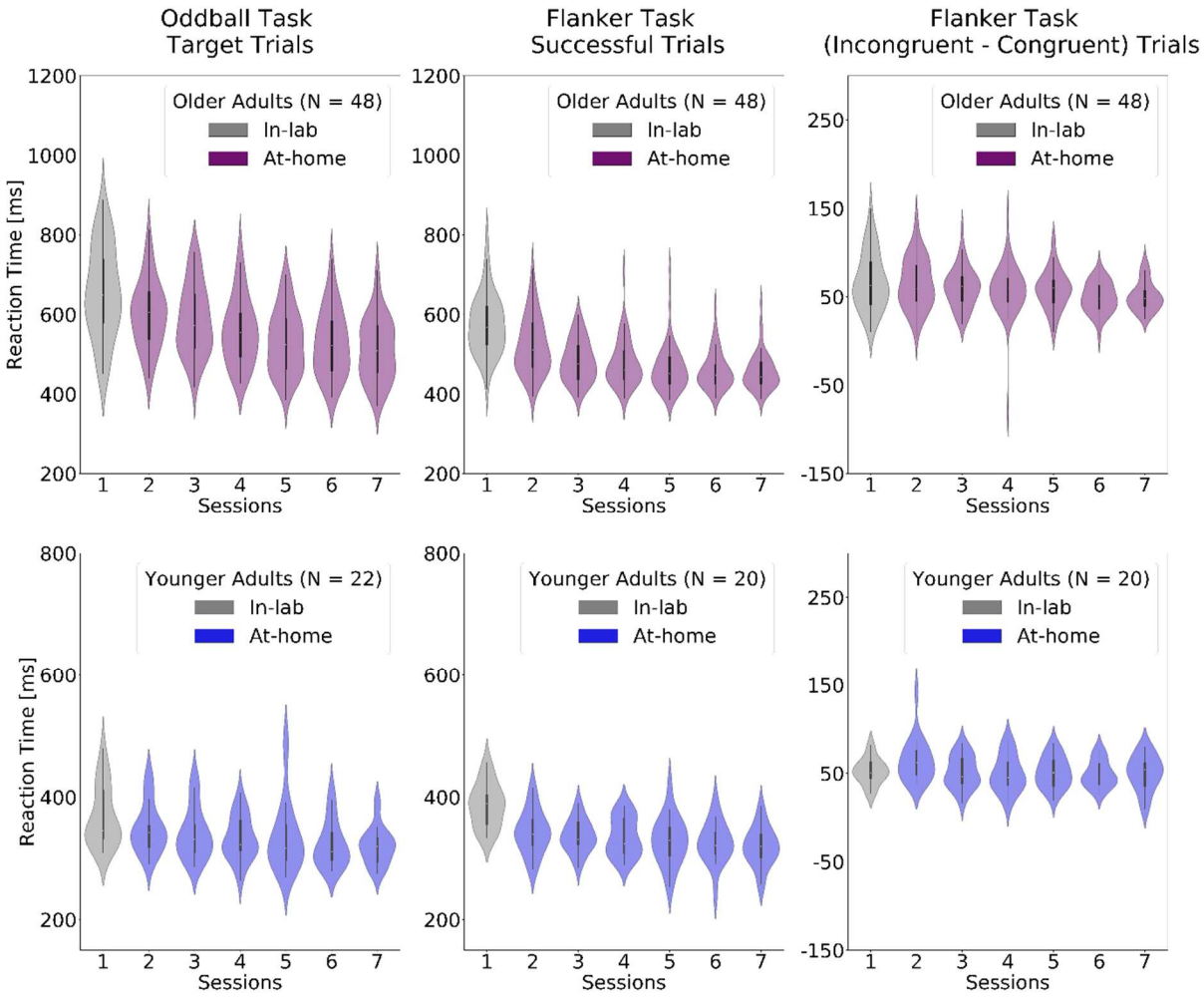


Figure 15: Behavioural responses to the gamified tasks during the first seven sessions in the Data of the Older Adult Study are depicted in purple (top row) and of the Younger Adult Study in blue (bottom row). From left to right: RT to the successful trials in the gamified Oddball task RT to the successful trials in the gamified Flanker task, difference in RT between the incongruent minus congruent successful trials in the gamified Flanker task (N older adults = 48, N younger adults = 20).

	Task and Behavioural Metric	Coef. (SE)		z-stat	P-values	95% Confidence Interval	Residual DFs
Older Adult Study	Oddball RT	Intercept	658.92 (11.95)	55.16	<software resolution	[635.02, 682.33]	341
		Slope	-22.87 (1.54)	-14.83	<10e-49	[-25.89, -19.85]	
	Flanker RT Successful trials	Intercept	562.36 (8.46)	66.49	<software resolution	[545.78, 578.93]	334
		Slope	-17.89 (1.01)	-17.65	<10e-69	[-19.87, -15.90]	
	Flanker Difference RT (Incongruent-Congruent) trials	Intercept	70.47 (3.28)	21.46	<10e-101	[64.03, 76.9]	334
		Slope	-3.03 (0.52)	-5.79	<10e-8	[-4.05, -2.00]	
Younger Adult Study	Oddball RT	Intercept	367.6 (8.56)	42.94	<software resolution	[350.82, 384.38]	150
		Slope	-7.24 (1.11)	-6.5	<10e-10	[-9.42, -5.06]	
	Flanker RT Successful trials	Intercept	374.89 (7.46)	50.25	<software resolution	[360.27, 389.51]	136
		Slope	-8.87 (0.9)	-9.85	<10e-22	[-10.63, -7.10]	
	Flanker Difference RT (Incongruent-Congruent) trials	Intercept	56.89 (4.10)	13.87	<10e-43	[48.86, 64.93]	136
		Slope	-1.05 (0.54)	-1.96	0.050	[-2.1, 0.001]	

Table 5: Linear mixed effect model estimates and Wald tests of behavioural data. Estimates of the fixed and random effects with their corresponding standard error (SE) and statistics of the individual estimates are provided.

3.3.4 EEG Results

3.3.4.1 EEG data collection success rate

Table 6 summarizes the number of trials collected for Oddball and Flanker tasks in the two studies and the wet EEG dataset, and how many of those trials survived epoch rejection to reach analysis at key electrode locations.

In some cases, all trials were rejected, and a session was not available for analysis. Of tasks for which the data was complete in the Younger Adult study, on average across all electrodes, 95% of the Oddball task sessions (SD = 5%, range: 82-100%) and 94% of the Flanker task sessions (SD = 6%, range: 83-99%) remained following pre-processing. In the Older Adult study, on average across all electrodes, 84% of completed Oddball task sessions (SD = 7%, range: 68-91%), and 85% of the Flanker task sessions (SD = 6%, range: 69-90%) were retained following pre-processing. All results are presented on Figure 16, and Tables 7 and 8.

To check that the number of trials rejected remained stable across sessions, I plotted the number of trials rejected across sessions at FCz and Pz in both cohorts. Percentages of trials rejected across sessions are presented on Figure 17. A summary of the number and percentage of available sessions at each step of the data analysis are presented in Table 7.

			Number of trials collected (SD, range)	Percentage of trial discarded (%) (SD, range)	Number of available trials after artefact rejections (SD, range)
Older Adult Study (N=50)	**Oddball task**	**Target Trials**	30	64.2 (26.5, 0-100)	10.7 (7.9, 0-30)
	Flanker Task	**Correct Trials[a]**	126.2 (4.8, 64-134)	73.9 (21.8, 6.5 -100)	32.6 (27.4, 0-117)
		Error Trials[a]	6.7 (4.1, 1-24)	61.9 (36.4, 0-100)	2.5 (2.8, 0-16)
Younger Adult Study (N=30)	**Oddball task**	**Target Trials**	30	43 (23.4,0-100)	17.1 (7, 0-30)
	Flanker Task	**Correct Trials[a]**	117.8 (9.6, 85-136)	59.3 (18.7, 4.7-100)	47.5 (21.9, 0-104)
		Error Trials[a]	20.2 (13.3, 1-64)	40 (24.7, 0-100)	11.3 (8.2, 0-39)
Wet EEG dataset (N=40; Kappenman et al. 2021)	**Oddball task**	**Target Trials**	40	23.69 (21.2, 0-87.5)	30.5 (8.5, 5-40)
	Flanker Task	**Correct Trials[b]**	352.1 (36.2, 182-398)	4.5 (7.3, 0-34.9)	337 (46.2, 151-390)
		Error Trials[b]	42 (22.4, 2-83)	4.3 (7.2, 0-33.3)	40.1 (21.4, 2-80)

Table 6: Mean number of available trials after processing and percentage of data discarded per session per participant. The number of trials passing quality control were computed at the Pz electrode for the Oddball task, and at the FCz electrode for the Flanker task. The wet EEG tasks lasted about 10 mins. The gamified Oddball and Flanker lasted about 12 and 7 mins, respectively. [a]150 trials were presented and could be answered correctly or incorrectly. [b]400 trials were presented and could be answered correctly or incorrectly.

	Oddball Task					
At-home sessions	*Older Adults*			*Younger Adults*[a]		
	Session	%	Cumulated %	Session	%	Cumulated %
Requested	725	100	100	390	100	100
Attempted	750	103.4	103.4	347	89.0	89.0
Task data complete	730	97.3	100.7	346	99.7	88.7
Survived epoch rejection[b]	634	86.8	87.4	339	98.0	86.9
	Flanker Task					
	Older Adults			*Younger Adults*[a]		
	Session	%	Cumulated %	Session	%	Cumulated %
Requested	725	100	100	390	100	100
Attempted	699	96.4	96.4	347	89.0	89.0
Task data complete	675	96.6	93.1	347	100.0	89.0
Survived epoch rejection[b]	577	85.5	79.6	339	97.7	86.9

Table 7: Number of available at-home sessions at each step of the data collection analysis, including percentage retained relative to previous step. The number of sessions that passed quality control were computed at the Pz electrode for the Oddball task, and at the FCz electrode for the Flanker task. [a]Only data collected before the infusion interventions are evaluated here, therefore percentages may vary somewhat relative to the figures cited in section 3.3.2. [b]All the epochs in a session could be rejected during this step.

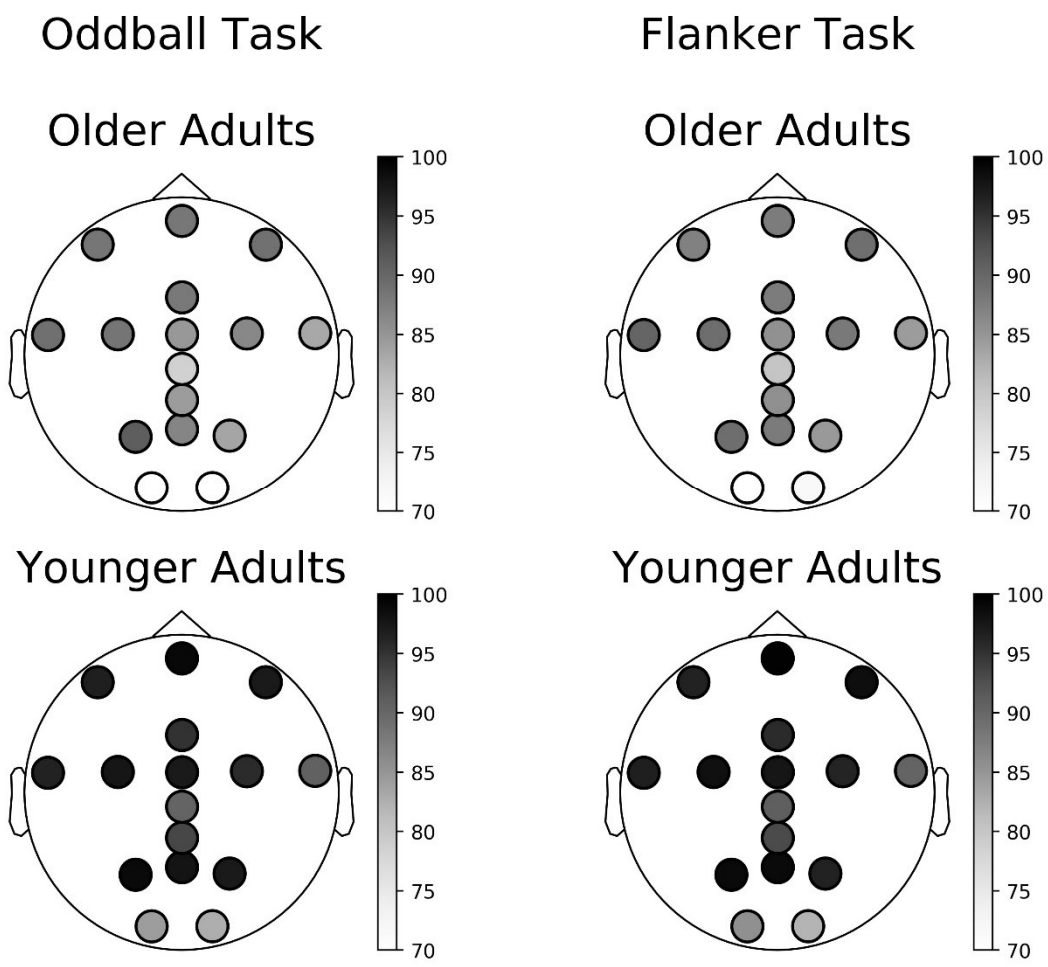


Figure 16: Percentage of available sessions after pre-processing per channel. The top row corresponds to data collected in the Older Adult study. The bottom row corresponds to data collected during the Younger Adult study. The left column of each figure corresponds to data collected during the gamified Oddball task, the right column of each quadrant to data collected during the gamified Flanker task.

Channel	*Oddball Task - Older Adults (N=50)*	*Oddball Task - Younger Adults[a] (N=30)*	*Flanker Task - Older Adults (N=50)*	*Flanker Task - Younger Adults[a] (N=30)*
O1	495	292	466	297
O2	505	286	482	285
Pz	634	339	593	343
P3	665	342	603	343
CPz	617	323	578	323
P4	610	337	572	335
Cz	574	313	541	316
FC3	647	338	603	341
FCz	619	337	577	339
FC4	631	331	595	334
Fz	643	329	592	332
FT7	650	334	610	336
AF7	646	335	589	335
Fpz	645	343	592	346
AF8	649	337	602	342
FT8	608	314	570	314
Average	**614.88**	**326.88**	**572.81**	**328.81**
Std Err.	**49.96**	**17.25**	**42.17**	**17.58**
Min	**495**	**286**	**466**	**285**
Max	**665**	**343**	**610**	**346**

Table 8: Count of usable sessions per channel. [a]Only data collected before the pharmacological interventions are evaluated here.

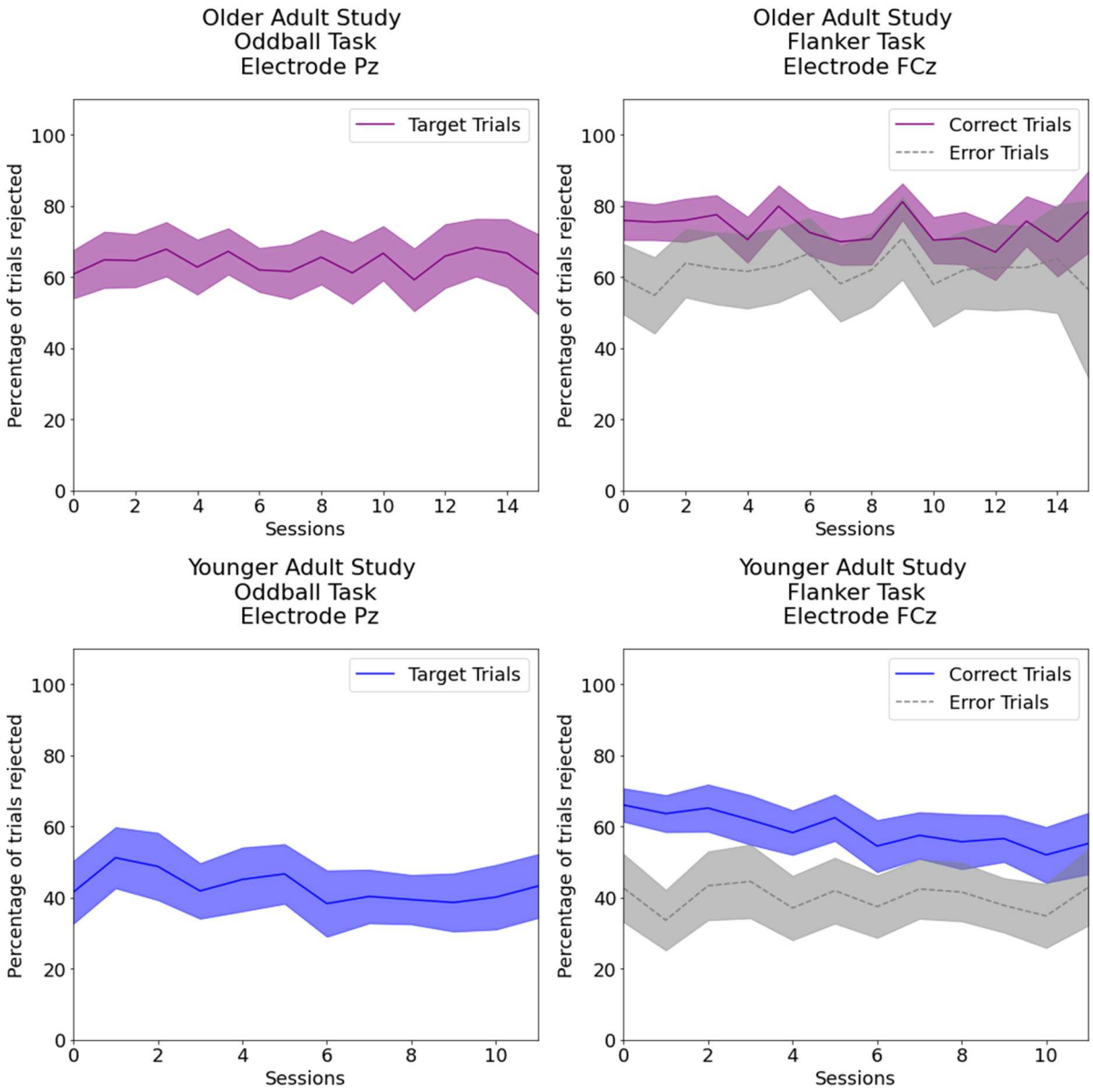


Figure 17: Mean percentage of trials rejected across time. Top row: Older Adult Study. Bottom Row: Younger Adult Study. Left Column: Target Trials extracted from the Oddball task. Right Column: Correct and Incorrect trials extracted from the Flanker tasks. Shaded areas correspond to the 95% confidence intervals.

3.3.4.2 Younger Adult Study

ERPs extracted from the Oddball and Flanker task of the Younger Adult Study are presented in the top row of Figure 18 and on Figures 20 to 23. The typical waveform features of a P300 ERP can be observed: negative readiness potentials, P2 and N2 components occurred from before 0 to 250ms,

followed by the P300 component peaking around 350ms. In the Flanker task, the expected positive deflections were observed after Correct Trials and negative deflection after Error trials around 50ms after participants' response.

The central row of Figure 18 projects what SME can be achieved by aggregating increasing numbers of trials per participant over multiple at-home dry sessions. As noted above, as that number increases, the number of participants that can be included in the sub-analysis decreases (as some participants may not have collected enough data to be included in the sub-analyses). The SME can be seen to decrease with the inverse of the root mean square of numbers of trials.

The wet EEG study (Kappenman *et al.*, 2021) reported achieving an SME of 1.83 μV based on the average of 30.5 Oddball target trials that survived their epoch rejection strategy (grey-dotted lines in the figure). Comparing that to data from our Younger adult at-home data, I found that 25 usable Target trials (i.e., from the pool that survived epoch rejection; red line in the figure) were required in the Younger Adult Study to reach an equivalent level of ERP variability (though with the higher rate of epoch rejection previously mentioned).

For the Flanker task, the wet EEG study reported achieving SME values of 0.51 μV and 1.68 μV for Correct and Error trials, respectively. I found that 317 usable Correct trials and 37 usable Error trials were required to reach the same SME values obtained with 337 usable Correct trials and 40 usable Error trials using a wet EEG system (all following epoch rejection).

The bottom row of Figure 18 shows the total number of experimental trials required to reach wet-EEG benchmark SME values for each ERP, and we can project from that to the number of at-home sessions to achieve or exceed that. For this study, which had a comparable cohort to the wet EEG dataset, we can project that 2 equivalent sessions of at-home gamified dry EEG would provide a superior SME (lower signal variability) than the single lab-based session for the Oddball Target—assuming the number of trials per session were the same in both studies. For the Flanker task, 3 dry EEG sessions would be sufficient for the Error trial ERP, and 2 sessions for the Correct trial ERP.

Figure 19 shows SME data from the in-laboratory sessions for both the Oddball and Flanker tasks. For all ERPs, the SME data extracted from the in-laboratory sessions were lower than the SME data extracted from at home sessions. When looking at data collected in the laboratory, 14 usable Target trials (e.g., that survived trial rejection) were required to reach an equivalent SME value obtained with 30.5 usable trials using a wet EEG system. When looking at the Flanker task, I found that 243 usable Correct trials and 19 usable Error trials were required to reach the same SME values obtained with 337 usable Correct trials and 40 usable Error trials using a wet EEG system.

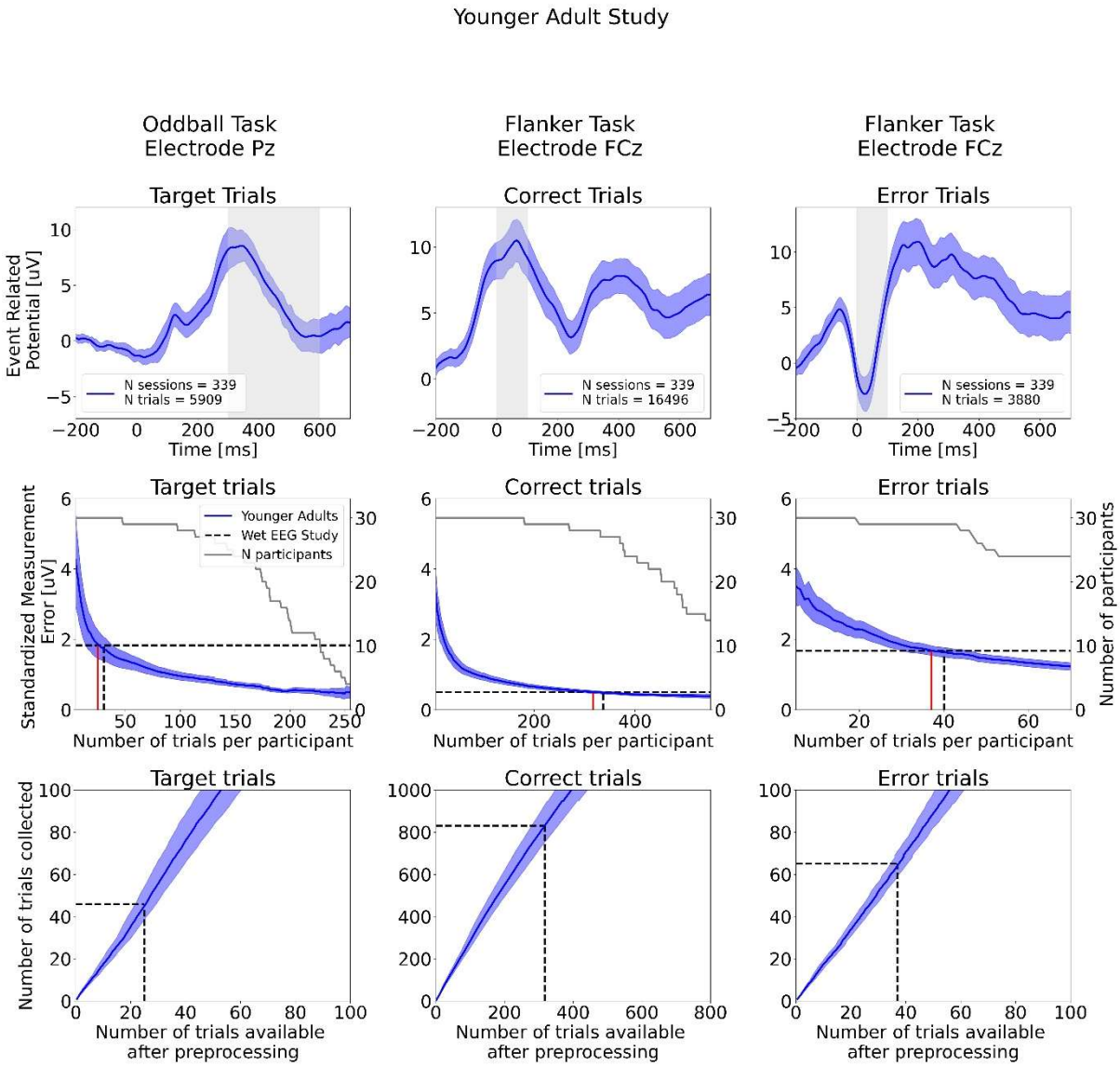


Figure 18: ERPs analyses extracted from the Younger Adult Study (N=30). Top row: Grand study average computed across all participants. Event-related potentials. Middle row: Standardized Measurement Errors per number of trials. The grey continuous lines correspond to the number of participants remaining in the SME calculation after trial rejection. Bottom Row: Mean numbers of trials available after preprocessing. The black dotted lines correspond to the mean numbers of trials extracted from the wet EEG study. From left to right: Target Trials extracted from the Oddball task at electrode Pz, Correct Trials extracted from the Flanker task at electrode FCz, Error Trials extracted from the Flanker task at electrode FCz. The shaded areas correspond to the 95% confidence intervals.

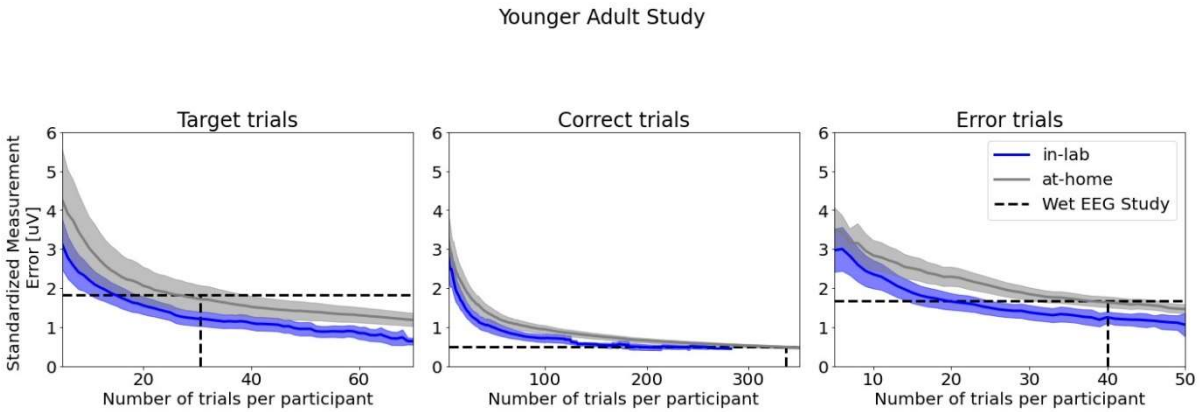


Figure 19: Standardized Measurement Errors per number of trials of data collected in the laboratory under researcher supervision extracted from the Younger Adult Study (N=30). The blue line corresponds to data collected in the laboratory. The grey line corresponds to data collected in the home. The black dotted lines correspond to the mean numbers of trials extracted from the wet EEG study. From left to right: Target Trials extracted from the Oddball task at electrode Pz, Correct Trials extracted from the Flanker task at electrode FCz, Error Trials extracted from the Flanker task at electrode FCz. The shaded areas correspond to the 95% confidence intervals.

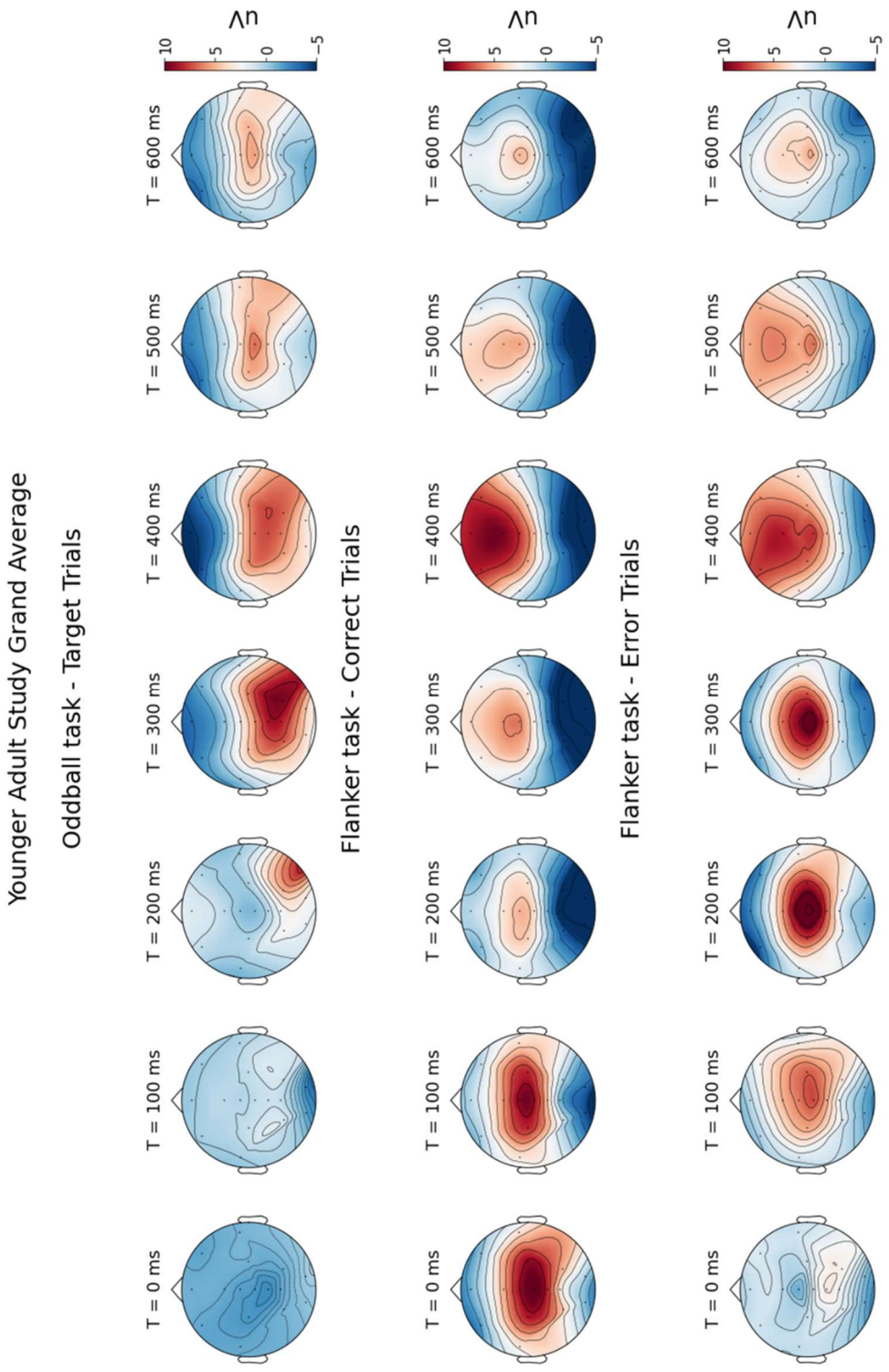


Figure 20: Topographic maps of the event-related potentials collected during the Younger Adult Study. Top row: ERPs extracted from the Oddball task locked to the Target stimulus presentation. Middle row: ERPs extracted from the Flanker task locked to participants' response to the Correct Trials. Bottom row: ERPs extracted from the Flanker task locked to participants' response to the Error Trials.

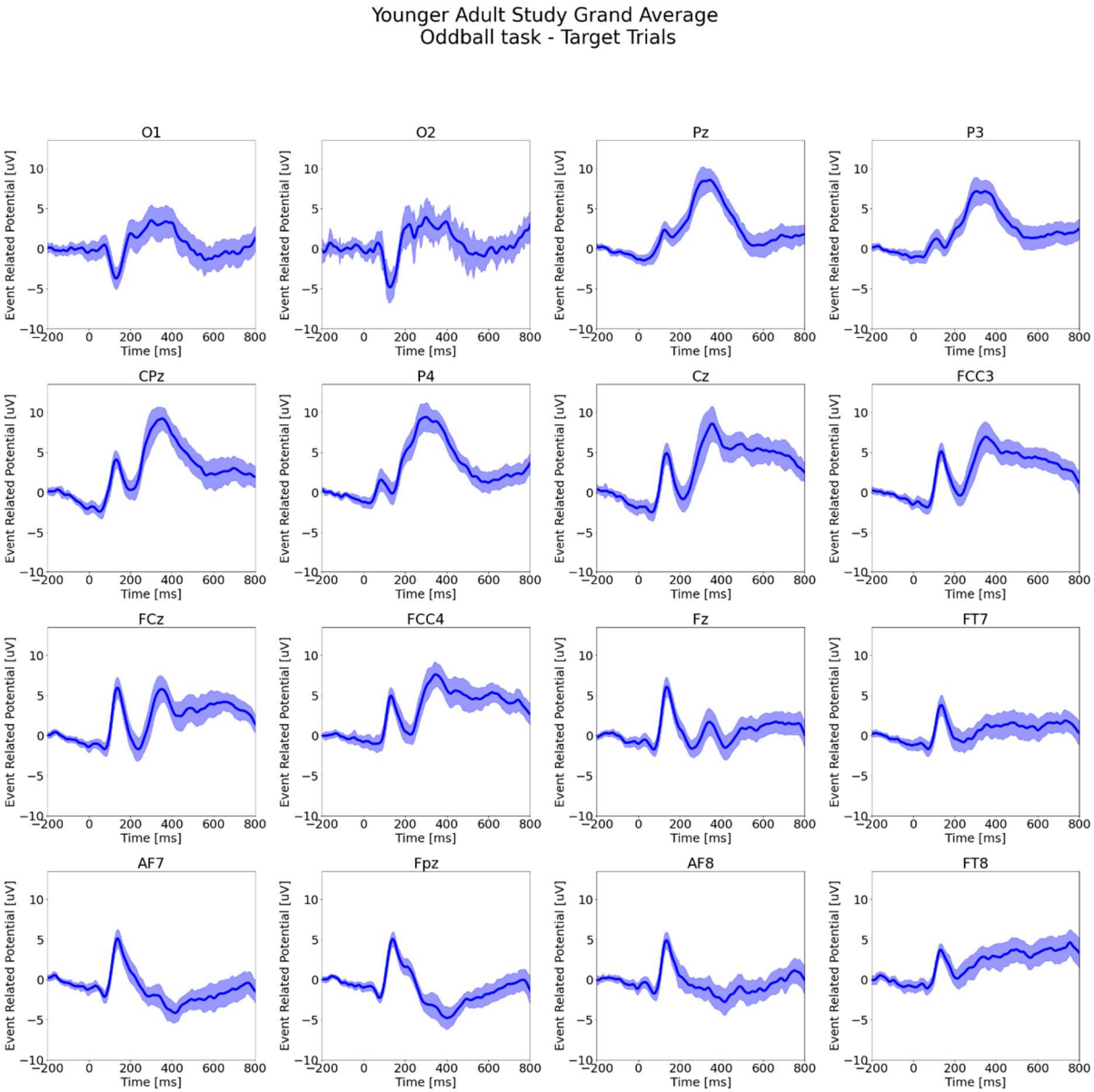


Figure 21: Event-related potentials collected during the Younger Adult Study extracted from the Oddball task locked to the Target stimulus presentation. From the top left plot to the bottom right plots: O1, O2, Pz, P3, CPz, P4 Cz, FC3, FCz, FC4, Fz, FT7, AF7, Fpz, AF8, and FT8. Shaded areas correspond to the 95% confidence intervals.

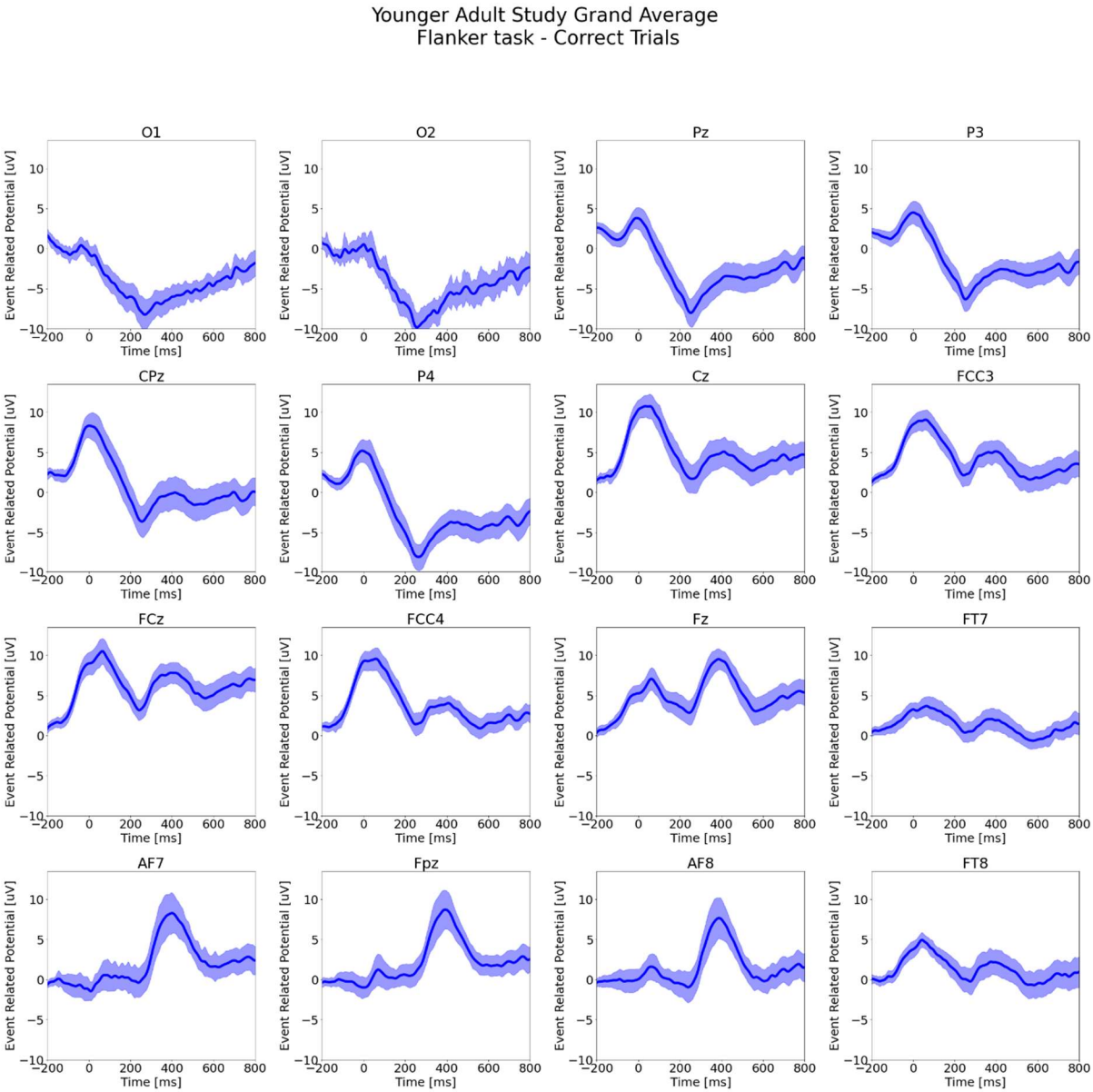


Figure 22: Event-related potentials collected during the Younger Adult Study extracted from the Flanker task locked to participants' response to the Correct Trials. From the top left plot to the bottom right plots: O1, O2, Pz, P3, CPz, P4 Cz, FC3, FCz, FC4, Fz, FT7, AF7, Fpz, AF8, and FT8. Shaded areas correspond to the 95% confidence intervals.

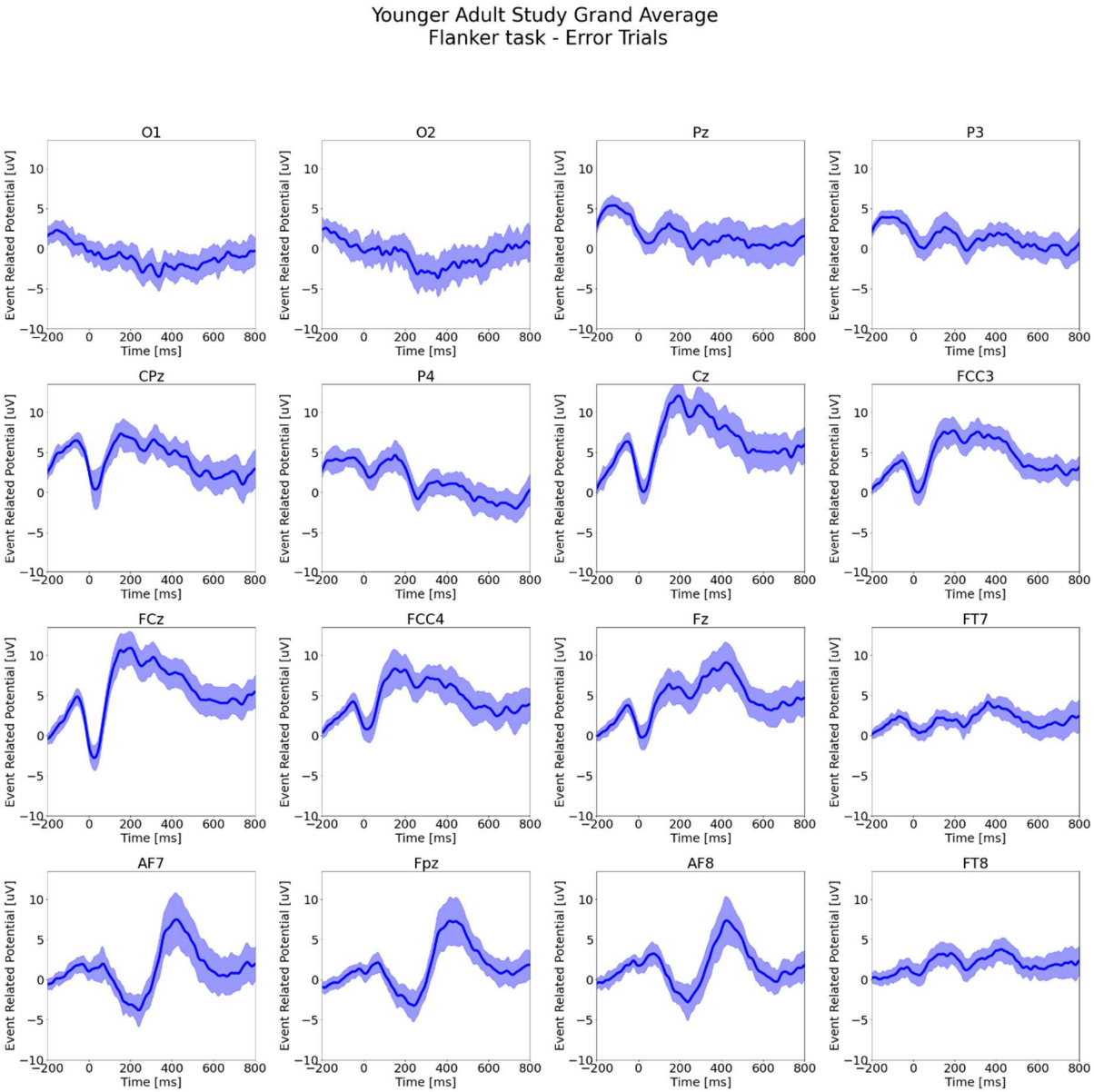


Figure 23: Event-related potentials collected during the Younger Adult Study extracted from the Flanker task locked to participants' response to the Correct Trials. From the top left plot to the bottom right plots: O1, O2, Pz, P3, CPz, P4 Cz, FC3, FCz, FC4, Fz, FT7, AF7, Fpz, AF8, and FT8. Shaded areas correspond to the 95% confidence intervals.

3.3.4.3 Older Adult Study

ERPs extracted from the Oddball and Flanker tasks from the Older Adult Study are presented in the top row of Figure 24 and ERPs at all electrodes are presented in Figures 26 to 29. As in the Younger Adult Study, Negative readiness potentials, P2 and N2 components occurred from before 0 to 250 ms, followed by the P300 component peaking a bit later compared to the younger adult at about 450 ms in the ERPs extracted from the Oddball task. As before, the expected positive deflection after Correct Trials and negative deflection were observed after Error trials around 50 ms after participants' response in the Flanker task data.

The central row of Figure 24 projects the SME that can be achieved in the Older Adult Study. When comparing with SME values extracted from the wet EEG study, 22 usable Target trials were required in the Older Adult Study to reach the same SME value obtained with 30.5 usable Target trials using the wet EEG system. For the Flanker task, 509 usable Correct trials and 47 usable Error trials were required to reach the same SME values obtained with 337 usable Correct trials and 40 usable Error trials in the wet EEG study. These numbers of trials correspond to trials available after epoch rejections.

The bottom row of Figure 24 shows the total number of experimental trials from our older cohort required to reach wet-EEG SME values from a younger cohort. Here, 2 dry at-home EEG sessions for the Oddball Target, 7 for Correct ERPs and 4 for Error ERPs in the Flanker task, would have provided a superior SME (lower signal variability) than the single laboratory-based session if the same number of trials were collected per session with the wet and dry EEG system.

Figure 25 shows SME data from the in-laboratory sessions for both the Oddball and Flanker tasks. For Target and Correct trials, the SME data extracted from the in-laboratory sessions were lower than he SME data extracted from at home sessions. When looking at data collected in the laboratory, 13 usable Target trials (e.g., that survived trial rejection) were required to reach an equivalent SME value obtained with 30.5 usable trials using a wet EEG system. In the case of the

Flanker task, it was not possible to perform the calculation as not enough usable trials were collected in the laboratory to match the SME values obtained with the wet EEG system.

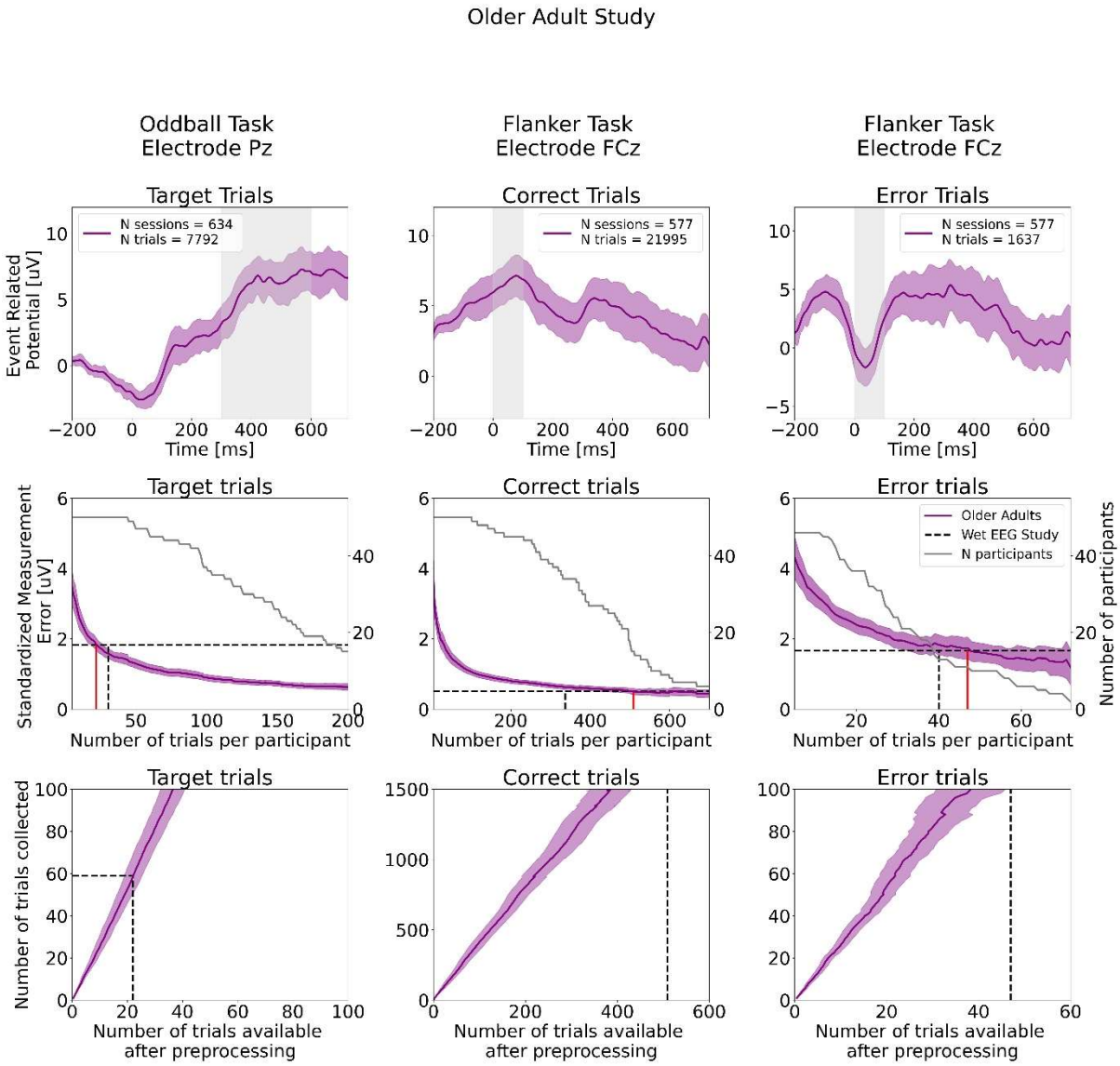


Figure 24: ERPs analyses extracted from the Older Adult Study (N=50). Top row: Event-related potentials. Middle row: Standardized Measurement Errors per number of trials. The grey continuous lines correspond to the number of participants remaining in the SME calculation after trial rejection. Bottom Row: Mean numbers of trials available after preprocessing. The black dotted lines correspond to the mean numbers of trials extracted from the wet EEG study. From left to right: Target Trials extracted from the Oddball task at electrode Pz, Correct Trials extracted from the Flanker task at electrode FCz, Error Trials extracted from the Flanker task at electrode FCz. The shaded areas correspond to the 95% confidence intervals.

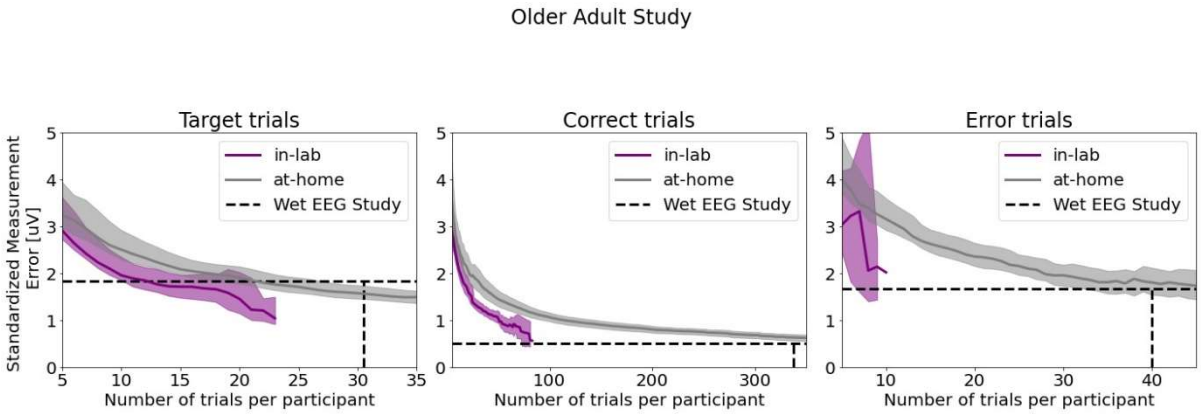


Figure 25: Standardized Measurement Errors per number of trials of data collected in the laboratory under researcher supervision extracted from the Older Adult Study (N=50). The purple line corresponds to data collected in the laboratory. The grey line corresponds to data collected in the home. The black dotted lines correspond to the mean numbers of trials extracted from the wet EEG study. From left to right: Target Trials extracted from the Oddball task at electrode Pz, Correct Trials extracted from the Flanker task at electrode FCz, Error Trials extracted from the Flanker task at electrode FCz. The shaded areas correspond to the 95% confidence intervals.

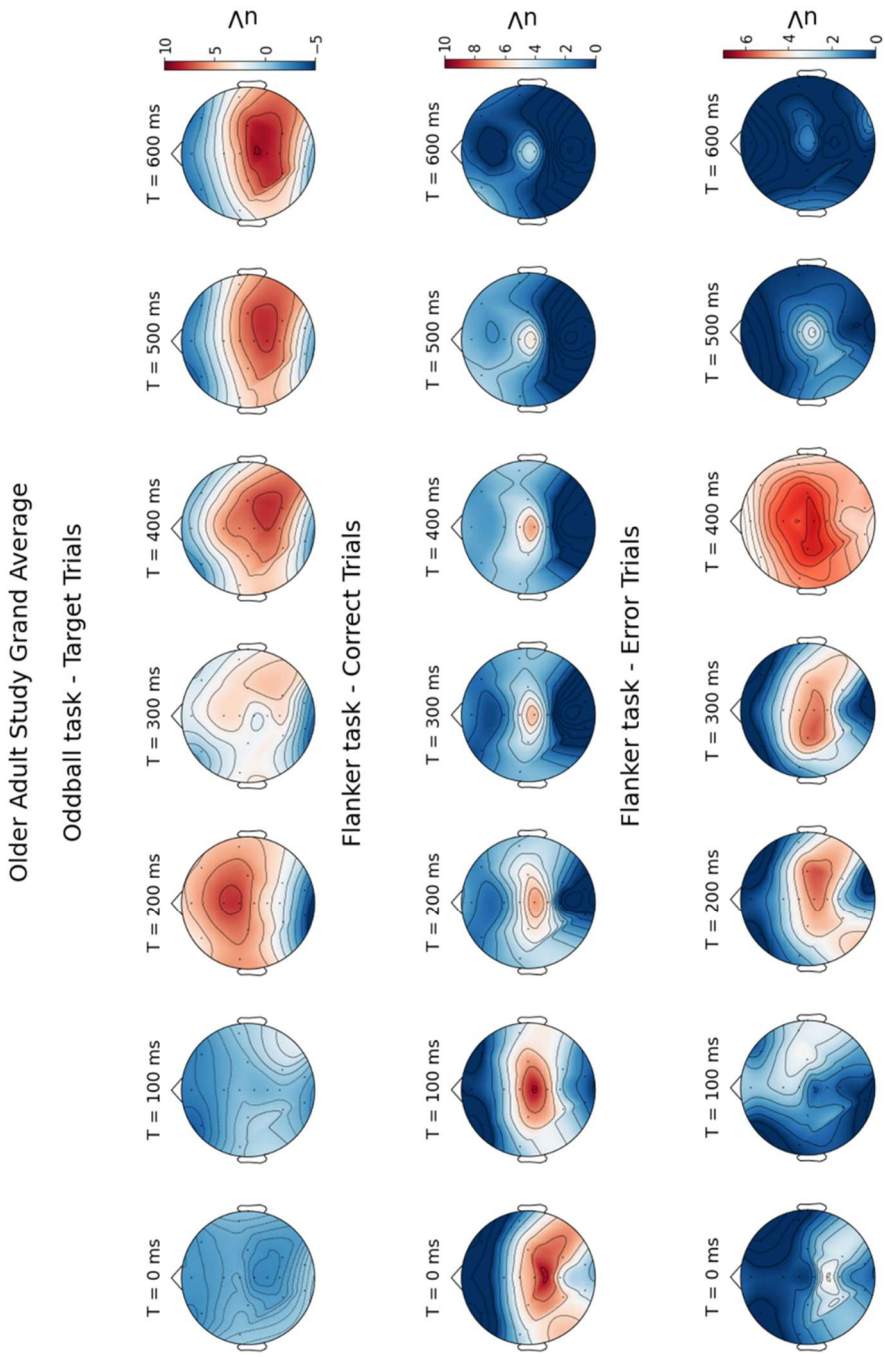


Figure 26: Topographic maps of the event-related potentials collected during the Younger Adult Study. Top row: ERPs extracted from the Oddball task locked to the Target stimulus presentation. Middle row: ERPs extracted from the Flanker task locked to participants' response to the Correct Trials. Bottom row: ERPs extracted from the Flanker task locked to participants' response to the Error Trials.

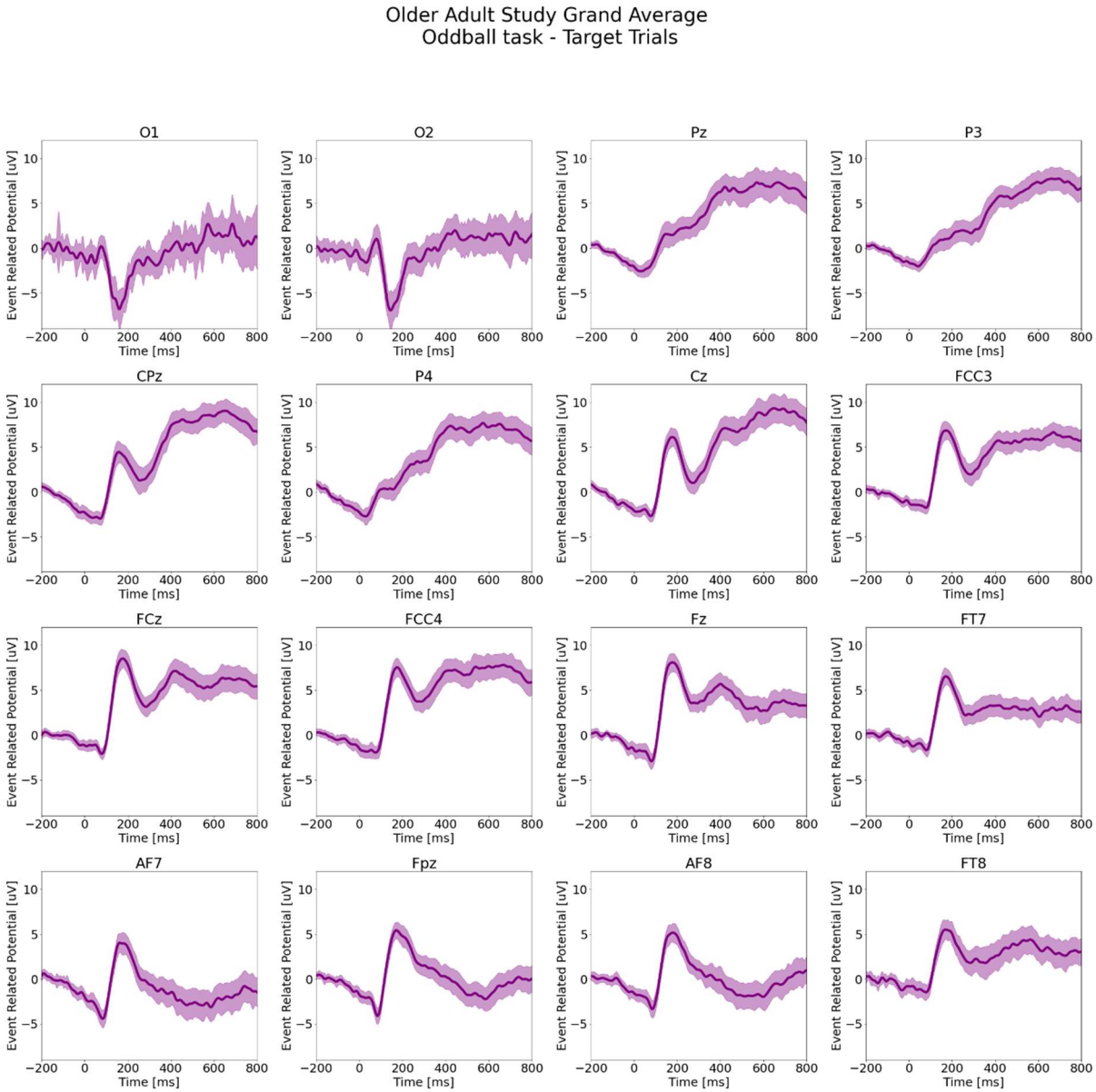


Figure 27: Event-related potentials collected during the Older Adult Study extracted from the Oddball task locked to the Target stimulus presentation. From the top left plot to the bottom right plots: O1, O2, Pz, P3, CPz, P4 Cz, FC3, FCz, FC4, Fz, FT7, AF7, Fpz, AF8, and FT8. Shaded areas correspond to the 95% confidence intervals.

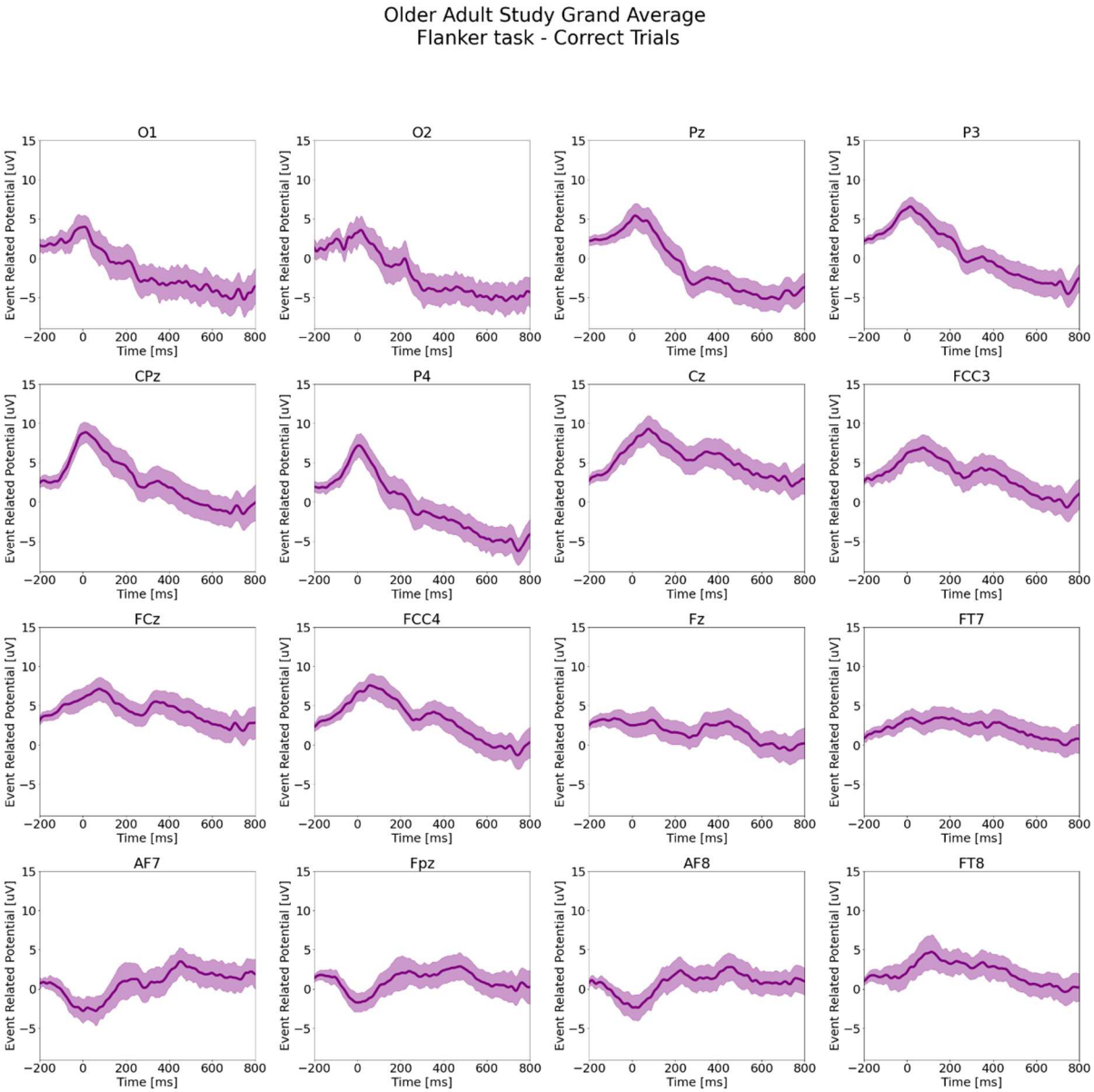


Figure 28: Event-related potentials collected during the Older Adult Study extracted from the Flanker task locked to participants' response to the Correct Trials. From the top left plot to the bottom right plots: O1, O2, Pz, P3, CPz, P4 Cz, FC3, FCz, FC4, Fz, FT7, AF7, Fpz, AF8, and FT8. Shaded areas correspond to the 95% confidence intervals.

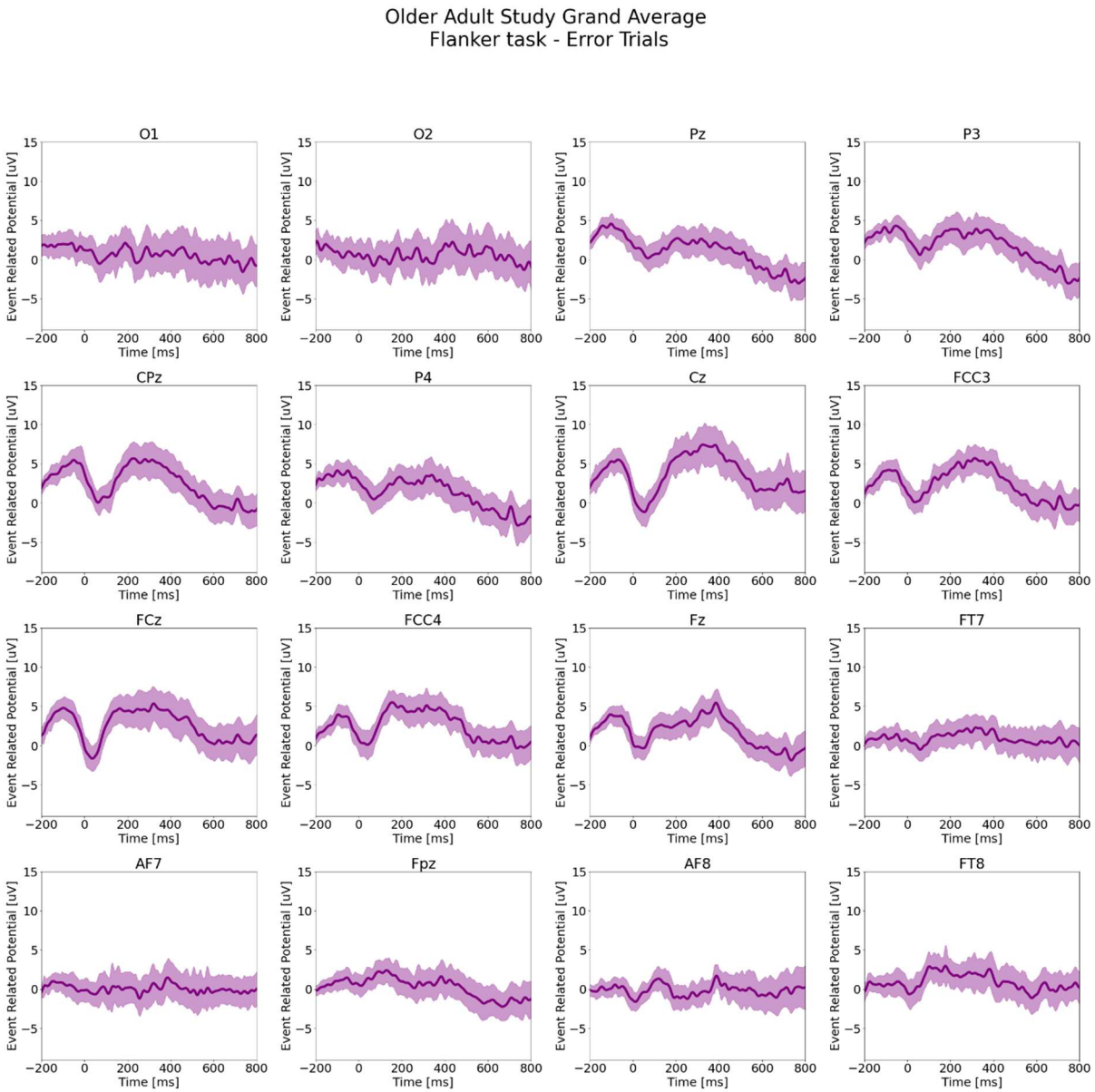


Figure 29: Event-related potentials collected during the Older Adult Study extracted from the Flanker task locked to participants' response to the Error Trials. From the top left plot to the bottom right plots: O1, O2, Pz, P3, CPz, P4 Cz, FC3, FCz, FC4, Fz, FT7, AF7, Fpz, AF8, and FT8. Shaded areas correspond to the 95% confidence intervals.

3.4 Discussion

The overall objective of this chapter was to evaluate if dry EEG recorded in the home by unsupervised participants, with easy-to-use engaging tasks, could yield datasets of the same

quality as published results derived from wet EEG recorded by an expert group in a controlled environment. The primary finding was that it was feasible to reach similar SMEs compared to a wet EEG study with the same numbers of dry trials when comparing populations of similar age. However, the percentage of trials discarded after artefact rejection was substantially higher in the dry system compared to what was reported in the wet EEG study used as reference. I also evaluated the recording platform usability using the participants' adherence to the protocol, successful data collection rate, and subjective reports. Participants reliably collected EEG data on a near-daily basis.

Participants exhibited high adherence to the dry EEG protocol: on average >94% of requested sessions were commenced in both cohorts. Notably, the compensation of each cohort was not pro-rated to the number of sessions session completed in the home. The older group were modestly compensated (€40) for the at-home study, whereas the younger group were paid €500 for their participation in the study: suggesting that monetary compensation alone was not the most important factor in adherence. There was a high rate (over 93%) of sessions successfully completed at home. Furthermore, the positive user feedback (mean SUS score >84 in the older cohort and >88 in the younger cohort; corresponding to 'good/excellent' ratings (J. Brooke, 1996)) demonstrated that participants, including older adults up to 81 years-old, did not appear to feel the lack of supervision of a trained technician to complete neurocognitive tasks.

The comparison of the ERP CORE wet EEG data evaluated participants of similar age profile to our younger adult cohort revealed that similar numbers of trials were required to reach the same SME values. However, on average (and as expected), more dry EEG trials were rejected during preprocessing (between 2 to 14 times more). This result demonstrates that applying stringent data rejection techniques to dry EEG data makes it possible to generate averaged ERPs trials similar to those collected in laboratory environments. When accounting for the number of trials lost during artefact rejection, my analyses suggest that between 2 to 3 at-home gamified dry EEG sessions

using the same tasks parameters would yield the same SMEs as the wet EEG system for comparable cohorts.

The percentage of data that survived the different data selection procedures varied as a function of cohorts, tasks, and electrode location. Overall, dry EEG data collected from older adults were noisier than data from younger adults: between 15 to 20% more trials were rejected during the data selection procedures. Further investigations are needed to disentangle the origin of these differences, but one working hypothesis is that it could be due to age-related impairment in manual dexterity (Carment *et al.*, 2018) and its effect on headset setup and electrode contact quality. When comparing Flanker data extracted from the Younger and Older Adult studies, I observed that on average, each older adult session yielded less data compared to the young one. Two factors seem to be driving this effect, on average: i) more data were rejected from the Older Adult study and ii) older adults committed 3 to 4 times fewer errors compared to younger adults. The latter result suggests that older adults may use different speed vs. accuracy trade-off strategies compared to younger adults (Ghisletta *et al.*, 2018) and this should be taken into consideration when planning for the number of trials to be collected in studies within older populations.

When comparing data collected in the laboratory under researcher supervision to data collected unsupervised in the home, I observed that on average, data collected in the laboratory were less noisy. This result suggests that a part of the variability observed in the at-home dataset was not related to the hardware itself but also originated from other sources such as the lack of expert supervision or controlled environment. These finding highlights that when evaluating novel portable technologies, it is crucial to evaluate the technology performance when used outside of the laboratory as the hardware specification alone will not yield a representative assessment. In remote studies, the researchers lack visibility of what is happening in the home, and little is known about what is causing the drop in data quality. More studies are needed on participants at-home behaviours to elucidate how they interact with the technology and identify what are the sensitive

steps in the data collection process. An idea could be to video record participants during their at-home sessions to see if the headset is worn correctly and verify that the participant is not distracted. This approach could inform future iteration of the technology to improve headset design or the user interface of the mobile application.

Finally, I also discovered that the yield of usable data varied as a function of the electrode location and that Cz, O1, and O2 yielded the lowest amounts of usable data, possibly due to individual variation in head shape and hair style. This result is consistent with previous findings from Fiedler and colleagues who examined the impedance of the same dry EEG electrodes as used in the Cumulus headset, though in the context of a different montage, and found that impedance varied with electrode placement (Fiedler *et al.*, 2018). They reported that the minimum force to achieve impedance below 1.3MOhms was lower at frontal compared to temporal positions, probably because of hair layer impeding the electrode-skin contact (Fiedler *et al.*, 2018). These results taken together suggest that some electrode location may be subject to higher impedance values and that future headset design should consider potential solutions to this problem such as adjusting the length of the pins, changing the morphology of the electrodes at these locations, or making the headset more adjustable.

The broader discussion of the implications of the chapter are discussed in section 6.2.1 of the general discussion.

4 Empirical Chapter 2

Acute and persistent electrophysiological responses to subanaesthetic ketamine recorded inside and outside the laboratory using a novel EEG platform

4.1 Introduction

The data analysed in this chapter was collected as part of a collaborative project run by the University of Magdeburg, Germany, and Cumulus Neuroscience ltd. Its objective was to establish a proof-of-concept evaluating the suitability of self-administered portable dry EEG technology for pharmacological research. Ketamine was chosen as the target compound as it is a well-known and safe treatment routinely used in clinical care for anaesthesia, pain relief, and in treatment of psychiatric disorders. Further, its effects on human and animal EEG have been extensively studied in the literature which made it very attractive as a test case for remote EEG study. I participated in this study as the main scientific lead of Cumulus Neuroscience. I co-designed the study with Cumulus's partners, supervised a team of three researchers and participated in the collection of the dry EEG dataset. I designed and implemented all the analyses presented in this chapter. The study was investigator-led by Prof. Dr. Martin Walter of the University of Magdeburg, Germany. Cumulus Neuroscience provided funding for the project, and collaborated with several other groups on the design (Prof. Dr. Martin Walter's research group, Dr. Max Bianchi of Ulysses Neuroscience ltd., Dublin; Dr. Patricio O'Donnell of Takeda Pharmaceuticals Inc., Cambridge, USA).

Ketamine is a non-competitive antagonist of NMDA receptor which has received FDA approval for treatment-resistant depression in 2019 (Kew and Kemp, 2005; Murrough, 2012; Murrough, Abdallah and Mathew, 2017). Preliminary data putatively shows positive effects on mood in treatment resistant patients within hours, with effects lasting for up to 2 weeks (Murrough, Abdallah and Mathew, 2017; Widman and McMahon, 2020). A growing body of evidence suggests that ketamine could reverse the homeostatic downregulation of glutamatergic synapses observed in depressed brain (Krystal, Sanacora and Duman, 2013; Walter, Li and Demenescu, 2014; Li *et al.*, 2017; Murrough, Abdallah and Mathew, 2017; Lisek, Zylinska and Boczek, 2020; Luscher, Feng and Jefferson, 2020). However, its exact mechanism of action remains unknown.

The current Excitatory:Inhibitory (E:I) imbalance/disinhibition hypothesis suggests that ketamine binds to NMDA receptors located on GABAergic interneurons and prevents the release of gamma-

aminobutyric acid (GABA) in the extra-cellular space, therefore inducing an up-regulation of excitatory pathways (Homayoun and Moghaddam, 2007; Carlén *et al.*, 2012; Scheidegger *et al.*, 2012; Shaw *et al.*, 2015; Lener *et al.*, 2017; Lisek, Zylinska and Boczek, 2020; Widman and McMahon, 2020). Concomitantly, rapid increases in glutamate transmission are observed at the synaptic cleft between interneurons and glutaminergic neurons (Walter, Li and Demenescu, 2014). This glutamate surge triggers an augmentation of AMPA receptor trafficking in the postsynaptic pyramidal neurons which in turn promote the synthesis of BDNF and synaptic proteins (Maeng *et al.*, 2008; Li *et al.*, 2010, 2017). NMDAR blockades by ketamine also regulates calcium influx in postsynaptic cells which further promote neuroplasticity. More specifically, calcium mediated signalling upregulates dendritic growth, arborization and axonal outgrowth (Zhang *et al.*, 2008; Lisek, Zylinska and Boczek, 2020), as well as mammalian target of rapamycin (mTOR) signalling, synapses number and function in the prefrontal cortex (Li *et al.*, 2010; Zhou *et al.*, 2014; Duman *et al.*, 2016).

A large body of research supports the involvement of the GABA system in the neurobiology of ketamine action. It is thought that the blockade of NMDA receptors on cortical GABAergic interneurons by ketamine promotes the activity of the associated pyramidal cells throughout a mechanism of disinhibition (Homayoun and Moghaddam, 2007; Carlén *et al.*, 2012; Scheidegger *et al.*, 2012; Shaw *et al.*, 2015; Lener *et al.*, 2017). The Pyramidal-Interneuron Gamma (PING) model suggests that the gamma frequency band can be used as an indicator of the cortical-excitation inhibition balance (Uhlhaas and Singer, 2012; Muthukumaraswamy *et al.*, 2015; Rivolta *et al.*, 2015; Thiebes *et al.*, 2018). Supporting this hypothesis, both pre-clinical (Homayoun and Moghaddam, 2007) and clinical studies using EEG and MEG technologies report increases in gamma band power during the acute phase of ketamine (Hong *et al.*, 2010; Muthukumaraswamy *et al.*, 2015; Shaw *et al.*, 2015; de la Salle *et al.*, 2016; Thiebes *et al.*, 2018). While the underlying mechanisms behind these are less well-understood, decreased activity in the alpha and beta bands are also reported in these studies. Modulations of the MMN amplitude and latency are as

well widely described during the short-lived acute psychomimetic phase occurring during and up to 2 hr after the ketamine infusion (Umbricht *et al.*, 2000; Heekeren *et al.*, 2008; Schmidt *et al.*, 2012; Rosburg and Kreitschmann-Andermahr, 2016). The difference in between the ERP elicited by standard vs. deviant stimuli (the MMN) is smaller in patients with a diagnosis of a major psychotic disorder than in controls (Light and Näätänen, 2013). Similar modulation of MMN is induced by ketamine administration, supporting the use of ketamine as a model for psychosis. MMN disruption is a translational marker which has also been demonstrated in rodent studies (Nagai *et al.*, 2013).

Another ERP likely relevant for the study of ketamine mechanism of action is the ERN. It is putatively generated by activity in the ACC (Salvadore *et al.*, 2010; Davelaar, 2013), an area which has been shown to be less sensitive to errors following ketamine administration (Honey et al., 2005). Several psychiatric disorders are known to modulate the functioning of the ACC and subsequently the manifestation of the ERN (Bush, Luu and Posner, 2000; Alain *et al.*, 2002; Fallgatter *et al.*, 2003; Rogers *et al.*, 2004). At subanaesthetic doses, ketamine induces robust working memory impairments and debilitates conflict and error monitoring during execution; therefore, one can expect general performance decrements in speed and accuracy, as well as a modulation of the distractor interference effect typically observed in the Flanker task (Honey *et al.*, 2003, 2005; Davelaar, 2013). As the Error-Related-Negativity (ERN) evoked by the Flanker task indexes error monitoring performance and is generated in the ACC, this electrophysiological response is expected to be attenuated. Finally, little research has been done on the effect of ketamine on the P300, though a certain number of studies report a disruptive effect of the drug on working and episodic memory (Hetem *et al.*, 2000; Honey *et al.*, 2003, 2005; Morgan *et al.*, 2004). Only a few studies have examined the P300 modulation triggered by ketamine and reported a decrease of the P300 amplitude during the acute effect phase (Oranje et al., 2000; Watson et al., 2009; Musso et al., 2011).

Ketamine is metabolized and cleared from the human body in 2 to 3 hrs (Farmer *et al.*, 2020), suggesting that its mechanism of action can be divided into an acute phase during which drug effects can be directly related to NMDAR occupancy, and a delayed phase (during the days following the infusion) relating to long term structural and functional changes in synaptic circuits and cell excitability observable long after drug blood levels have fallen below any active threshold (Walter, Li and Demenescu, 2014; Widman and McMahon, 2020). Characterizing the individual states of ketamine's multiphasic response is of key interest as it would allow for the optimizing of a repeated dose regime, narrowing the plasticity window, and unravelling dose-response relationship at the individual level (Walter, Li and Demenescu, 2014). In this chapter, I aimed to address this problem by analysing a frequent at-home and in-laboratory EEG collection protocol utilizing a novel wireless recording platform that can be operated repeatedly by naïve participants unsupervised in the home. The primary objective of this chapter was to evaluate if supervised dry EEG in the laboratory could capture the well-known acute effects of ketamine on brain activity and cognition as described in the wet EEG literature. The second objective of this study was exploratory and evaluated if at-home unsupervised self-administered dry EEG could capture persistent effects of a low dose of ketamine on brain activity and cognition. I targeted well established ketamine EEG biomarkers including the MMN, gamma and alpha band power modulations (Umbricht *et al.*, 2000; Heekeren *et al.*, 2008; Schmidt *et al.*, 2012; Muthukumaraswamy *et al.*, 2015; Shaw *et al.*, 2015; de la Salle *et al.*, 2016; Thiebes *et al.*, 2018). MMN was elicited before and after ketamine administration as well as during the acute phase, with the expectation that it would be reduced in amplitude during acute administration relative to before and after. Additionally, EEG biomarkers that have been associated with the ACC and Prefrontal Cortex (PFC) activities (e.g., the Event-Related Negativity – ERN; and the P300) were included in the analyses (Yeung, Botvinick and Cohen, 2004; O'Connell et al., 2007; Polich, 2007; Baker and Holroyd, 2011; Yeung and Summerfield, 2012; Kirschner et al., 2021). To the best of my

knowledge this will be the first time that self-administered dry EEG recording will be used in a pharmacological challenge study to characterize multiphasic brain responses to ketamine.

In this chapter, in a double-blinded design, 30 young healthy males received randomized and counterbalanced injections of ketamine or saline before and after completing repeated self-administered EEG enhanced cognitive tasks either in the clinics or in the home. They were asked to attend for two infusion sessions, 4 weeks apart. Task-driven and passive EEG was recorded in the laboratory directly before, during and after infusion, as well as 24 hrs later. Each infusion day was preceded by a week of at-home unsupervised EEG recording, to establish a baseline, and followed by a week of at-home recording to capture any persistent patterns of change in the EEG. My main hypotheses were that I would emulate the results of the ketamine wet EEG literature. Specifically, I expected to observe increases in gamma power, decreases in alpha power and a disruption of the MMN signal during and immediately after the ketamine infusion compared to the saline condition. I expected these effects to be short lived, with a return to baseline after 24 hrs. When examining EEG biomarkers associated with the ACC and PFC, I hypothesized that the psychomimetic effects of ketamine would trigger transient disruption of the ERN and P300. No a priori hypotheses were made on direction of changes in the days after the infusions.

	Passive Auditory Oddball	Active Visual 2-Stimulus Oddball	Flanker Task	Eyes-Closed Resting State
Cognitive function	Pre-attentive sensory memory	Attention and decision making	Attention, inhibition and error-awareness	*not applicable*
Behavioural Effects	*not applicable*	Impaired decision making (lower accuracy, slower reaction times)	Impaired cognitive control (lower accuracy, slower reaction times)	*not applicable*
EEG Effects	Decrease in MMN amplitude	Decrease in the P300 amplitude	Exploratory analyses of ERN disruption	Disruption of Alpha and Beta, Increase in Gamma power
Main Electrodes of interest	Fz, FCz	Cz, Pz	Cz	Whole Scalp
Time window of main interest in the time series	125-225 ms post stimulus	300-600 ms post target stimulus	0-100 ms post Participants' response	Throughout the infusion
Protocol Time Points	During infusion and 1 hr post infusion	1 hr post infusion	1 hr and 24 hrs post infusion	During infusion and 1hr post infusion

Table 9: Hypothesised effects as suggested by the literature.

4.2 Methods

4.2.1 Participants Study Design

The description of the study protocol as well as the one of the participants is provided in section 2.1.1 of this thesis. Briefly, this study was a saline-controlled, double-blind, randomized, cross-over study with healthy participants, designed to investigate the acute and delayed effects of ketamine on EEG and behavioural measures. Participants were invited to the laboratory on several different occasions to complete repeated measurements: at enrolment, and before and immediately after, and 24hrs after each infusion. The two infusions took place four weeks apart following the same study protocol, while administration of ketamine or saline was crossed-over. Throughout the study, additional cognitive testing and EEG data collection was remotely performed by participants unsupervised in the home, for a week period prior to and after each infusion sessions (four weeks in total). All EEG recordings were performed with the portable dry EEG platform developed by Cumulus. The details of the study protocol are described in section 2.1.1 of this thesis while the details of the dry EEG platform are provided in section 2.2.

4.2.2 Investigational and Control Products

The compounds and the source are detailed below in Table 10.

	Investigational Product	Control Product
Trade Name	Ketamine Inresa	Berlin-Chemie Isotone NaCl 0,9% Glas Inj.-Lsg.
Name of Active Ingredient	Ketamine	Saline
Form	Solution for Injection	Solution for Injection
Dose or Concentration	50 ml (0.5mg/kg body weight)	50 ml (0.9 %)
Manufacturer (Name and address)	Inresa Arzneimittel GmbH Obere Hardtstraße 18 79114 Freiburg	Berlin-Chemie, Glienicker Weg 125-127, 12489 Berlin www.berlin-chemie.com/Home

Table 10: Investigational and control compounds used.

4.2.2.1 Clinician-Administered and Self-Report Data

Seventeen questionnaires were administered during the study to establish the participants' psychological and personality profiles, and to quantify subjective experience of the ketamine infusion. The detailed list of the questionnaires can be found in Table 11. I focused in this report on 2 questionnaires out of the 17, the Clinician-Administered Dissociative States Scale (CADSS) and Montgomery-Åsberg Depression Rating Scale (MADRS) to contrast my quantitative analyses with subjective reports of ketamine effect. Results extracted from the remaining questionnaires will be analysed in future reports. All questionnaires used validated German-language versions, except for the CADSS questionnaire which was translated by the research team as no validated translation was available.

4.2.2.2 Clinician-Administered Dissociative States Scale (CADSS)

As a measure of behavioural response to ketamine treatment, the study clinician administered an adapted version of the Clinician-Administered Dissociative States Scale (CADSS) (Bremner *et al.*, 1998) before infusion, one hour after infusion, and 24 hrs after infusion. The version used in this study consisted of 23 subject-rated items, which covered different experiences that the subject may have had at the time of assessment (e.g., seeing things moving in slow motion, feeling disconnected from their own body or distortions in auditory sensations). The participants choose from five possible responses, ranging from 0 (not at all) to 4 (extremely). Subscales of the CADSS are defined as the sums of particular sets of items, depending on a priori hypotheses for signs of amnesia, depersonalization, and derealization (Bremner *et al.*, 1998). As no validated German translation of the CADSS was available, the original validated CADSS questionnaire was translated by the research team and administrated by the study doctor who used the same language for each participant.

4.2.2.3 Montgomery-Åsberg Depression Rating Scale (MADRS)

The 10-item Montgomery-Åsberg Depression Rating Scale (MADRS) has been developed to detect changes in depressive symptoms under antidepressant treatment (Montgomery and Asberg,

1979). To reveal potential antidepressant effects of ketamine in the participants, baseline MADRS score was assessed before infusion, and consecutive scores were determined one hour after infusion and 24 hrs after infusion in both in-laboratory sessions. The items represent prevalent core symptoms of depression and are rated by a clinician based on a clinical interview. The rater decides on a score from a list of given scale steps (0, 2, 4, 6) but may also choose ratings that lie in between (1, 3, 5), where 0 indicates no observation of the symptom and 6 indicates observation of the symptom in an extreme form. Traditionally, the following threshold scores are suggested: 0 – 6 (symptom absent), 7 – 19 (mild depression), 20 – 34 (moderate depression), and >34 (severe depression) (Snaith *et al.*, 1995).

Questionnaires	Description of the measures	Setting, timepoints	Method of administration	References
BSA Questionnaire	Measurement of Physical and Sport Activity	completed in the home	Self-administrated	(Fuchs *et al.*, 2015)
Cognitive Style Questionnaire –Short Form German Version (CSQ-SF-DE)	Assessment of hopeless cognitive styles in depression research	completed in the home	Self-administrated	(Huys *et al.*, 2016)
Childhood trauma questionnaire (CTQ)	Self-report ratings covering the severity of emotional, physical, and sexual abuse and neglect during childhood	completed in the home	Self-administrated	(Wingenfeld *et al.*, 2010)
Multidimensional Assessment of Interoceptive Awareness (MAIA)	Multidimensional self-report measure of interoceptive body awareness	completed in the home	Self-administrated	(Mehling *et al.*, 2012; Reis, 2019)
Munich ChronoType Questionnaire (MCTQ)	Chronotype estimation	completed in the home	Self-administrated	(Roenneberg, Wirz-Justice and Merrow, 2003)
Pittsburgh Sleep Quality Index (PSQI)	Self-rated questionnaire which assesses sleep quality and disturbances	completed in the home	Self-administrated	(Buysse *et al.*, 1989)
State-Trait Anxiety Inventory Trait questionnaire (STAI-T)	Psychological inventory measuring anxiety level	completed in the home	Self-administrated	(Spielberger *et al.*, 1983)
Toronto Alexithymia Scale (TAS-20)	Measures of difficulties identifying and describing one's own feelings	completed in the home	Self-administrated	(Bagby, Taylor and Parker, 1994)
Temperament and Character Inventory (TCI-20)	Inventory of personality trait	completed in the home	Self-administrated	(Cloninger, Svrakic and Przybeck, 1993)
Brief Psychiatric Ratting Scale (BPRS)	Clinical scale to measure psychiatric symptoms	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Clinician administered	(Overall and Gorham, 1962)
The Clinician administered Dissociative States Scale (CADSS)	Measures of dissociative states	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Clinician administered	(Bremner *et al.*, 1998)
Montgomery Asberg Depression Scale (MADRS)	Measures of depressive symptoms	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Clinician administered	(Montgomery and Asberg, 1979; Snaith *et al.*, 1986)
Positive and Negative Affect Schedule (PANAS)	Mood scale comprising the Positive and Negative Affect Schedule.	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Self-administrated	(Watson, Clark and Tellegen, 1988; Janke and Glöckner-Rist, 2014)
Regensburg Insomnia Scale (RIS)	Rating scale for the assessment of psychological symptoms and sleep in insomnia	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Self-administrated	(Crönlein *et al.*, 2013)
Snaith-Hamilton-Pleasure-Scale (SHAPS)	Assessment of self-reported anhedonia	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Self-administrated	(Franz *et al.*, 1998)
State-Trait Anxiety Inventory Trait questionnaire (STAI-S)	Psychological inventory measuring anxiety level	In-laboratory: -1hr, +1.5hr, +24hrs relative to infusions	Self-administrated	(Spielberger *et al.*, 1983)
5D-ABZ	Questionnaire for the assessment of altered states of consciousness	In-laboratory: +1.5hr relative to infusions	Self-administrated	(Dittrich, Lamparter and Maurer, 2006)

Table 11: List of the questionnaires administered in the study.

4.2.3 Ketamine metabolites

The plasma sample preparation and analyses were conducted by a third-party service provider commissioned by Cumulus Neuroscience Ltd (see Appendix 8.1). Data analyses presented here and carried out within the context of this thesis consisted in computing the descriptive statistics presented in the results sections.

4.2.4 Behavioural Analyses

Due to the different sequence of events and nature of the data collected in the laboratory under experimenters' supervision compared to in the home, I analysed data collected in the laboratory and in the home separately. Reaction times (RT) to Target trials were extracted from the Oddball Task. Reaction times to Correct trials and the difference of reaction times between Incongruent minus Congruent trials were extracted from the Flanker task. Linear mixed-effects (LME) models were used to investigate the effect of ketamine on RTs. I chose to model the in-laboratory session as categorical fixed effects as I did not predict any monotonic linear effect between the baseline, the infusions, and the excretion of ketamine. To analyse the at-home data, I chose to model the sessions as continuous fixed effects as there was no intervention in the week following the infusion. Finally in these models, participants were random intercepts, drug was a fixed effect, and the interaction between session and drug was computed. This analysis was conducted using the Statsmodels package (version 0.10.1; https://www.statsmodels.org/devel/mixed_linear.html) in Python (version 3.6.9). Normality of the residuals' distribution was assessed by visual inspection.

4.2.5 EEG Analyses

4.2.5.1 EEG pre-processing

The EEG pre-processing procedure and ERP epoching strategies applied here are described in section 2.2.4 of this thesis. A summary of the key parameters of interest as well as the electrodes examined can be found in Table 12.

ERP Component	Electrode Site	Time-locking Event	Baseline Period	Time-window statistical analyses
P300 Target	Cz, Pz	Stimulus-locked	-200 to 0ms	300 to 600ms
ERN	FCz, Cz	Response-Locked	-400 to -200ms	0 to 100ms
MMN	Fz, FCz	Stimulus-locked	-200 to 0ms	125 to 225ms

Table 12: Electrode sites, time-locking event and baseline period for each component.

For spectral analyses, a short-term Fourier transform was used to compute an estimate of time-varying spectral power across resting state in eyes-closed conditions. For comparative purposes with literature, a normalization was applied before performing spectral density (PSD) analyses, and each window was divided by the mean power between the 5-35Hz to maximize capacity to detect changes in relative spectral power/shape. For the time points outside of the infusion time window, the PSDs were computed on 5-min eyes-closed resting state EEG sections. During the infusion, the resting state data comprised a 20-min eyes-closed EEG data section. Only the second half of the resting state data collected during the infusion were analysed as I expected the ketamine effects to build-up over time as the ketamine plasma concentration increased and to be maximum toward the end of the infusion.

4.2.5.2 EEG statistical analyses

Statistical analyses of PSDs and time series EEG were computed using a Statistical Parametric Mapping (SPM) approach computed in Python (version 3.6.9) using the SPM1D packages (version 0.4.8, https://spm1d.org/). SPM1D uses random field theory to make statistical inferences regarding registered (normalized) sets of 1D measurements and account for multiple comparisons across frequency- and time-series (Pataky, 2012, 2016). This approach allowed me to conduct mass univariate analyses for both PSDs data and EEG time series that consisted in a point-by-point

analyses corrected for multiple comparisons. It enabled the direct comparison of vectors of frequency- and time-series across different conditions without having to peak picks or compute mean amplitudes. For all analyses, thresholds of significance were corrected using a Bonferroni approach to account for repeated testing across multiple electrodes, that is alpha = 0.05/n were used if n electrodes were examined at the same time within the same task. Only participants who had usable data for all the different time points of interest were included in the analyses (i.e., participants for whom any one session was discarded during the previous preprocessing steps were excluded altogether). For each analysis, I report this number. Separate analyses were computed for at-home and in-clinic data as data collected in the home without supervision were noisier and aggregated to increase statistical power (i.e., see noise levels analyses from Empirical Chapter 1 in section 3.3.4). For data collected in the laboratory, I analysed the following timepoints: before, 1 hr after and 24 hrs after the infusion. For data collected in the home, I focused my analyses on the following aggregates: the 4 days before, Day 2 to Day 4 and Day 5 to Day 7 after the infusions.

4.2.5.2.1 During ketamine infusion

Mean normalized band powers extracted from the ketamine and saline conditions during the second half of the infusions (i.e., across the last 10 mins of the eyes closed recordings completed during the first 20 mins of the 40-min-long infusion, see Figure 7) were analysed using a one-sided paired t-test as I had pre-defined hypotheses on the directions of changes. Decrease in alpha band power was tested across the 7 to 14 Hz frequency at electrode Pz. Beta and Gamma band power increases were tested across the frequency range 20 to 40 Hz at electrodes Fz and FCz. These choices were guided by the literature and corresponds to the electrodes at which each signal of interest has been reported to be maximal (Rivolta *et al.*, 2015; Lozano-Soldevilla, 2018).

4.2.5.2.2 Peri-infusions

Resting state data collected before and after the infusions were analysed using a two-way repeated-measures ANOVA across three times-points (before infusion vs. 1hr after infusion vs.

24hr after infusion) and the two-drug condition (ketamine vs. saline). Alpha band power modulation was tested across the 7 to 14 Hz frequency at electrode Pz. Beta and Gamma band power modulations were tested across the frequency range 20 to 40 Hz at electrodes Fz and FCz.

The ERN and P300 signals were analysed using a two-way repeated-measures ANOVA across three times-points (before vs. 1hr after vs. 24hr after the infusions) and the two-drug condition (ketamine vs. saline). The MMN was analysed using a two-way repeated-measures ANOVA across four times-points (before vs. during vs. 1hr after vs. 24hr after the infusions) and the two-drug condition (ketamine vs. saline). MMN Analyses were restricted to the electrode Fz and FCz and to the predefined time window of interest: from 125 to 225 ms post-stimulus presentation. Analyses of the ERN were restricted to the electrodes Fz and FCz across the predefined time windows of interest: from 0 to 100 ms post participants responses. The P300 analyses were restricted to electrodes Cz and Pz and to the predefined time window of interest: from 300 to 600 ms post-stimulus presentation. These choices were guided by the literature and corresponds to the time-window at which each signal of interest has been reported to be maximal (Kappenman *et al.*, 2021).

4.3 Results

4.3.1 Recruitment

A total of 41 male participants were phone screened, of which 5 were not recruited either because they reported they would not be able to adhere to the protocol study or did not attend their study appointment. Consequently, 36 people were enrolled and underwent medical screening. Of those, 2 participants were excluded for medical reasons. A further 4 participants withdrew early in the study for the following reasons: 1 did not tolerate the headset, 1 expressed discomfort with blood draws, 1 feared taking ketamine, and 1 due to sickness. 30 participants (mean age = 25.5, SD = 3.6) participated in the study to completion.

	Mean	SD
Age in years	25.57	3.74
BMI	23.60	2.40
MADRS at baseline	0.27	0.69
CADSS at baseline	0.0	0.0
	N	**%**
Students	25	83
Previous Ketamine Use	10	33

Table 13: Summary table of the demographics of the participants

4.3.2 Protocol adherence

The adherence of participants to the study protocol was remotely monitored throughout the duration of the study via web dashboards. Members of the research team completed daily checks of the dashboard to monitor whether the tasks were being completed, that session data was being successfully collected from tablets, and that EEG data quality was adequate. When something abnormal was detected by the research team, the local research project leader contacted participants to enquire about any challenges and provide them with additional guidance. The total number of sessions completed is reported in Table 14. On average, participants completed between 5.6 and 6.3 sessions per week during the four at-home phases of the study. Across all participants, 36 at-home sessions were skipped out of the 690 initially targeted (see Table 14). In total more than 800 hrs of EEG data were collected.

	Total number of sessions collected	Total number of sessions requested per participant	Mean session submitted per participant (std dev.)	Missed sessions	Number of participants who missed sessions
At-home, before 1st infusion	192	6	6.3 (1.4)	6	5
At-home, after 1st infusion	199	5	6.4 (1.6)	6	4
At-home, before 2nd infusion	202	7	6.7 (0.9)	11	8
At-home, after 2nd infusion	173	5	5.6 (1.1)	13	9
In-laboratory sessions	270	9	9 (0)	0	0
Total	1036	32	34.4	36	16

Table 14: Summary table of the EEG recordings collected during the research study. "Missed" refers to when a participant was scheduled to complete a session but did not.

Post-infusion EEG sessions started on average 1.1 hrs after the beginning of the infusions, or approximately 25 mins after the infusion ended; following blood draws at around 0.9 hrs after the start of infusion. The EEG collected the day following the infusions was recorded on average 26.5 hrs after the infusions and the blood draws were taken after 25.9 hrs.

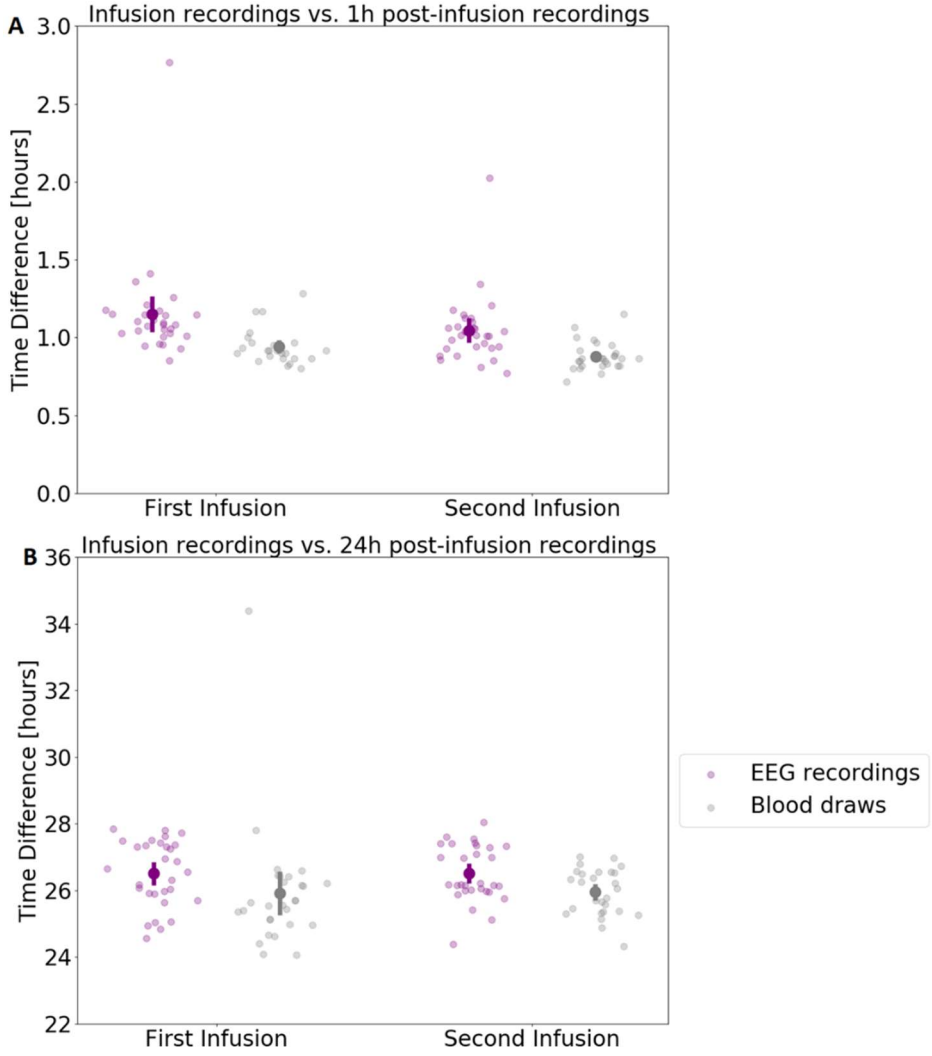


Figure 30: Precision in time spacing between infusion and post-infusion sessions (EEG and blood draws). A] Time delays between the data collected during the infusion compared to the 1-hr time point after the infusions. The purple data corresponds to the EEG recordings and the grey ones to the blood draws. **B]** Time delays between the data collected during the infusion compared to the 24-hr time point after the infusions. The purple data corresponds to the EEG recordings and the grey ones to the blood draws. The error bars correspond to the 95% confidence interval.

4.3.3 Self-reported effects of dissociation and mood

The participants' subjective dissociative effects reports were captured immediately before, immediately after and 24 hrs after each infusion via the CADSS questionnaire. To evaluate whether the drug order impacted their subjective experience, I first separately examined responses from the subgroup of participants that received ketamine first from the ones receiving the saline infusion first. Results are presented on Figure 31. First, I observe a striking difference between the overall reports after saline and ketamine infusions which suggests that participants could easily distinguish between the two conditions. Supporting this hypothesis further, I also observe that when comparing the ketamine first to the saline first sub-cohort, no participants that received ketamine first reported a dissociative effect after the saline infusion. When looking at the reports after the ketamine infusion, I observe that many participants reported dissociative symptoms an hour after the infusions but not 24 hrs after the infusion. This result is consistent with the literature reporting short lived psychotomimetic effects of ketamine (Walter, Li and Demenescu, 2014).

The participants' subjective levels of depression were also captured through the MADRS questionnaire at the same time points (i.e., before, immediately after and 24 hrs after the infusions.). Results are presented on Figures 32 and 33. Beside one outlier that did not exhibit consistent scores across the saline and infusion days, all participants scored below the threshold for mild depression before each infusion. I also note that after the ketamine infusion, participants reported higher rates of depressive symptoms, reaching "mild" levels according to conventional thresholds. However, this appears to be an artefact attributable to questionnaire items which are confounded with dissociative effects. An item-wise analysis of the MADRS scores indicated that concentration difficulties and inertia items dominated. 24 hrs after the infusion, these effects had dissipated for all participants but one, who was still slightly above threshold.

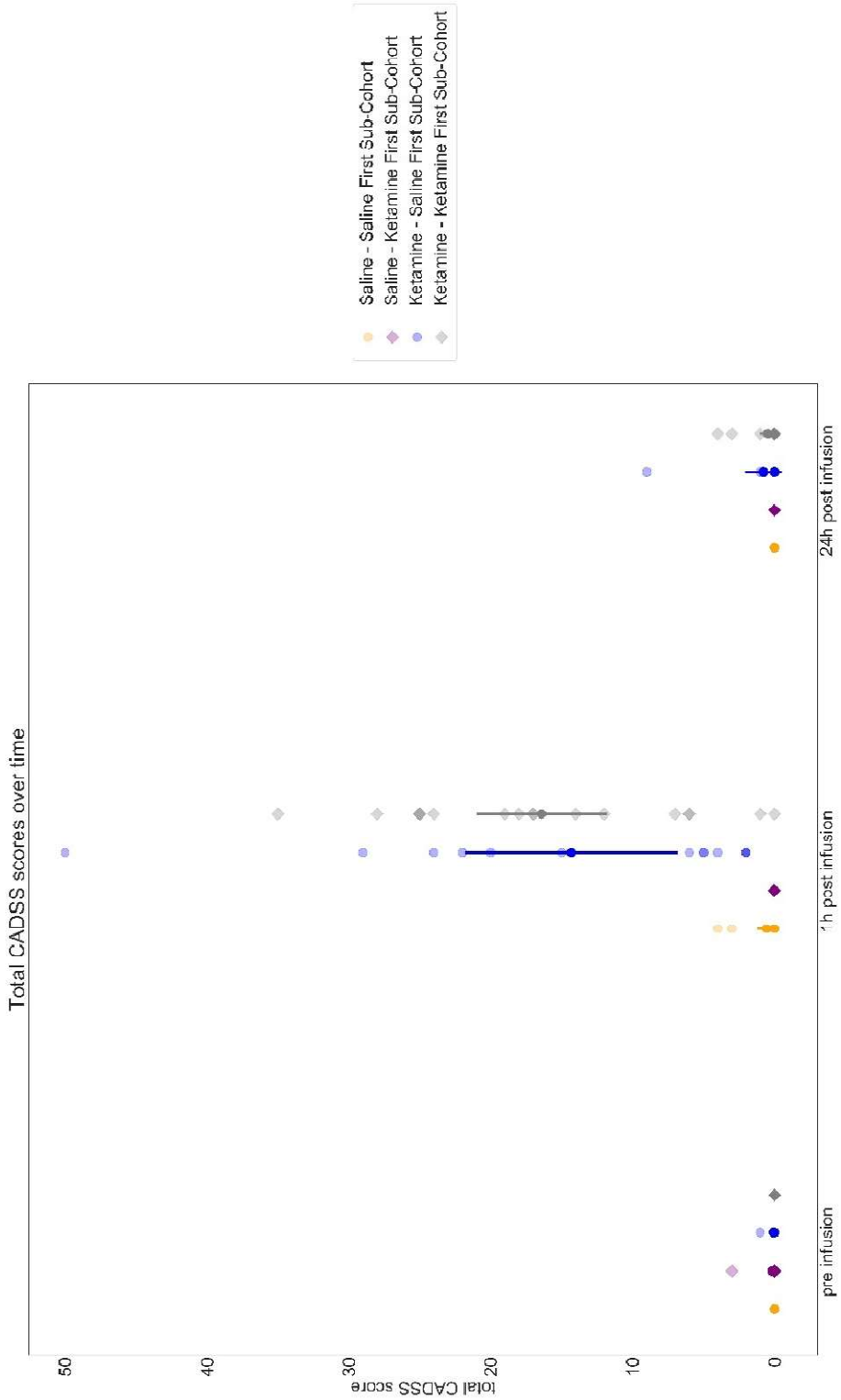


Figure 31: CADSS scores before, an hour after and 24h hrs after the ketamine and saline infusions. Data are presented separately for the ketamine first and saline first sub-cohorts. The circles represent the saline first sub-cohort (N=13) and the diamonds represent the ketamine first sub-cohort (N=17).

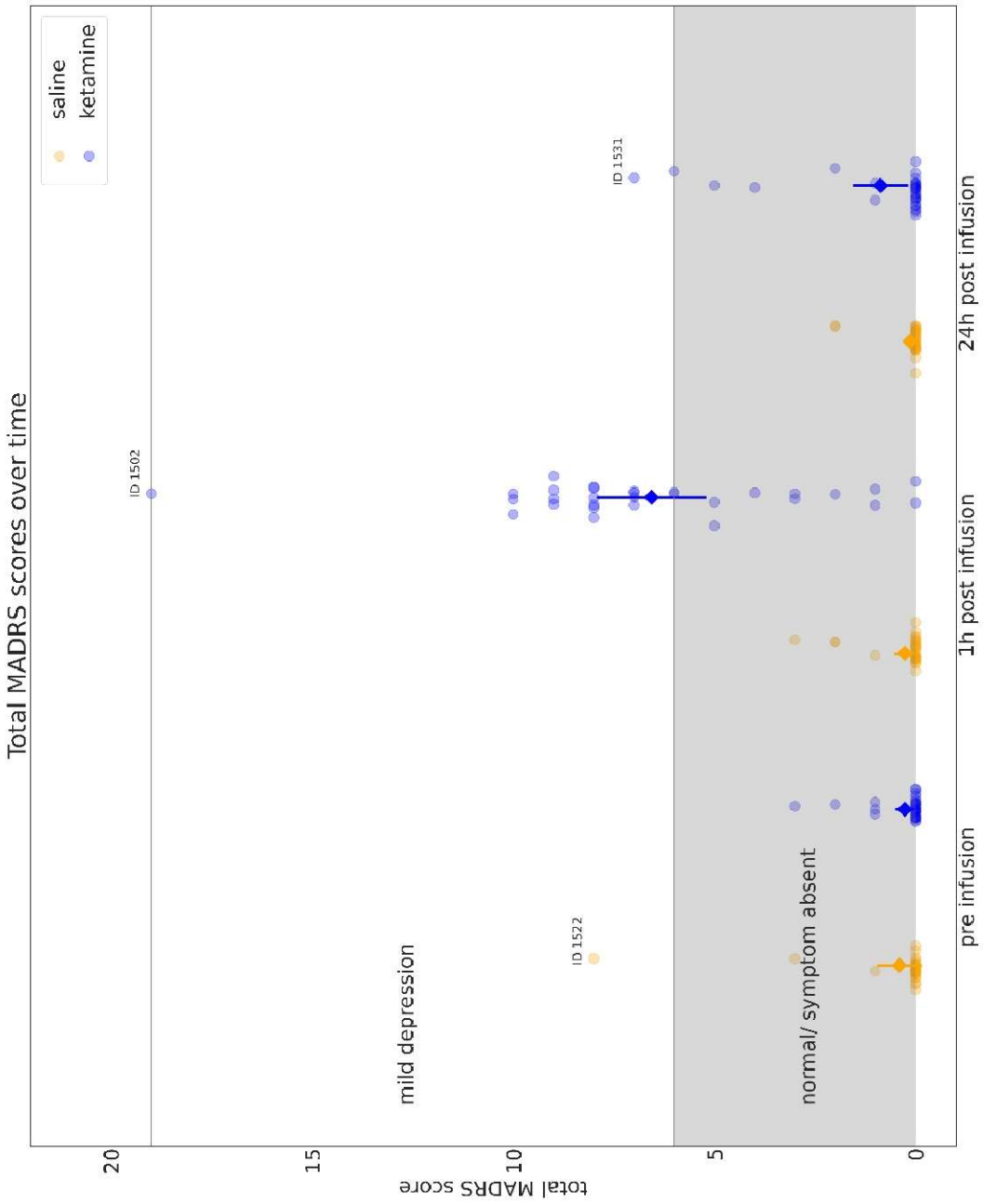


Figure 32: MADRS scores before, an hour after and 24h hrs after the ketamine and saline infusions. Data are presented separately for the saline and ketamine conditions. Subjects with maximum values are indicated for each timepoint. The range between total scores of 0 and 6 is defined as 'symptom absent', the range between 7 and 19 is defined as 'mild depression'. Diamonds represent sample means and the 95% confidence intervals are indicated.

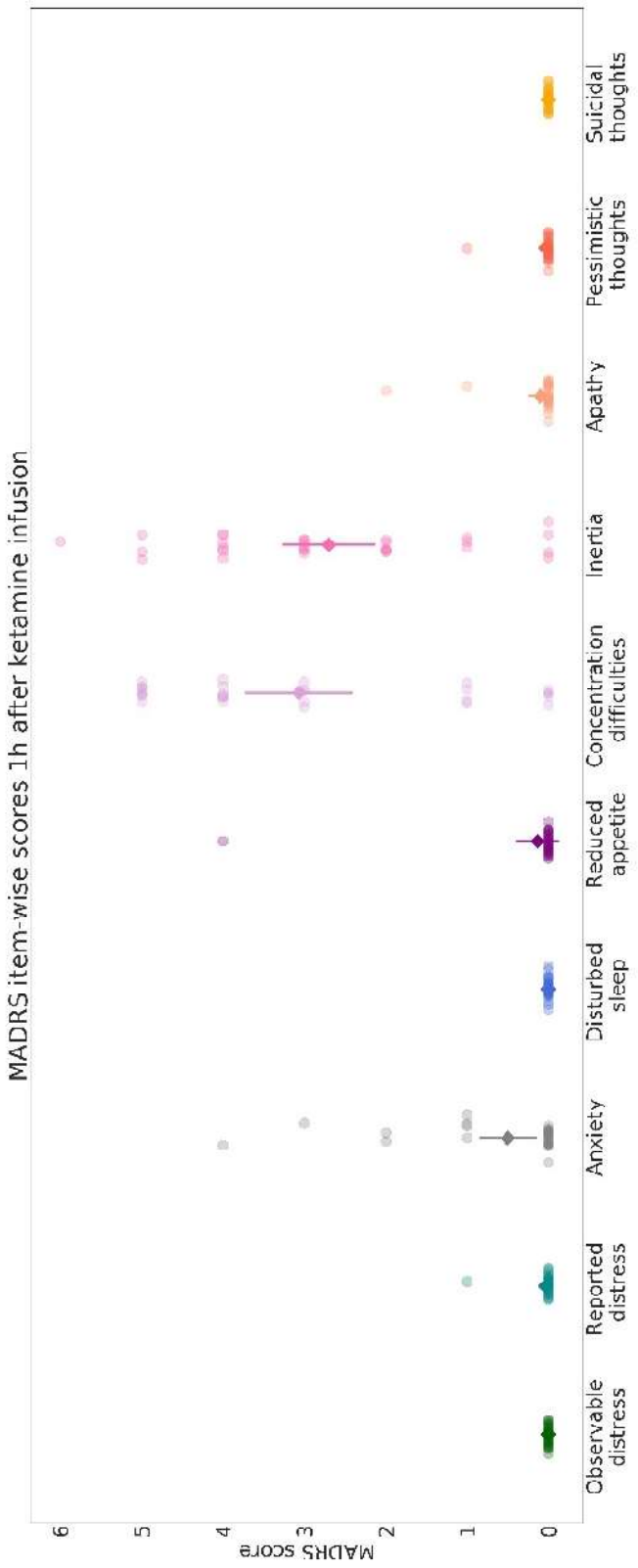


Figure 33: Item-wise MADRS scores one hour after ketamine infusion. Individual scores (0-6) are presented for each of the ten items of the MADRS questionnaire. Diamonds represent sample means and the 95% confidence intervals are indicated.

4.3.4 Ketamine metabolites

Analyses of the plasma concentrations of ketamine and its metabolite were conducted 20 mins and 40 mins after the beginning of the infusion. Data are presented on Figures 34 to 36. Results are consistent with the literature as I can observe that the ketamine plasma concentration is falling around ~180 ng/mL at the 40 mins time point and around ~130 ng/mL at the 20 mins timepoint (Horacek *et al.*, 2010). I also observe that the norketamine concentration is larger than the one of the hydroxy-ketamine at both time point which is consistent with the literature describing the ketamine is first metabolized in norketamine which is in turn metabolized in hydroxy-norketamine (Zarate *et al.*, 2012; Farmer *et al.*, 2020).

	Mean concentrations at t = 20 mins (ng/mL)	Mean concentrations at t = 40 mins (ng/mL)
Ketamine	128.7 (SD=72.8)	180.5 (SD=58.8)
Norketamine	16.2 (SD=13.8)	49.2 (SD=27.6)
Hydroxy-norketamine	11.0 (SD=40.7)	21.7 (SD=48.6)

Table 15: Plasma concentration of ketamine, norketamine and hydroxy-norketamine 20 mins and 40 mins after the beginning of the infusion. Data falling outside of the 10 to 90% quantiles were excluded.

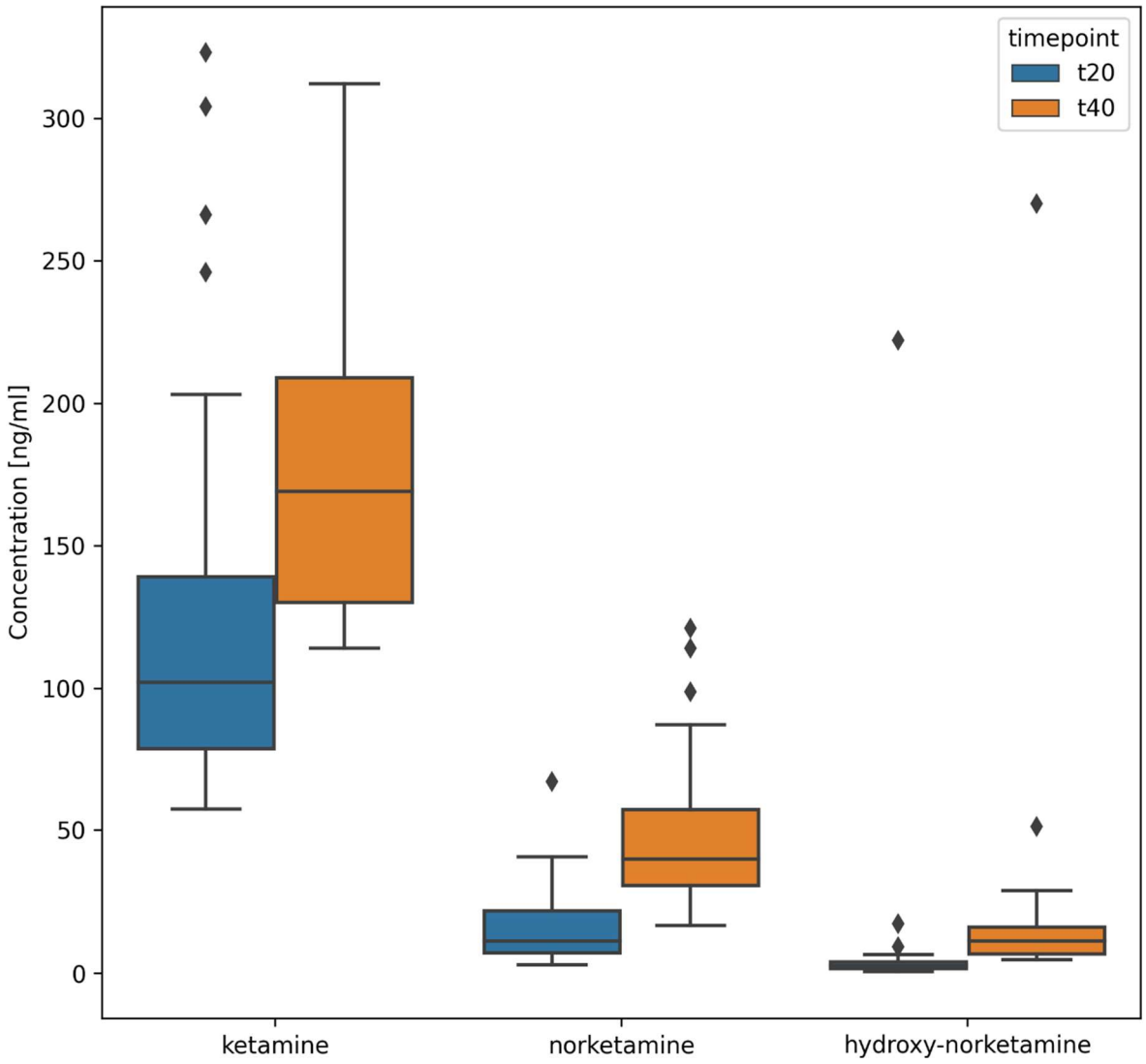


Figure 34: Boxplot of the evolution of the plasma concentration of ketamine and its metabolites 20 and 40 mins after the beginning of the infusion. Data corresponding to the 20 mins time point are presented in blue, the one corresponding to the 40 mins time point in orange. Data falling outside of the 10 to 90% quantiles were excluded.

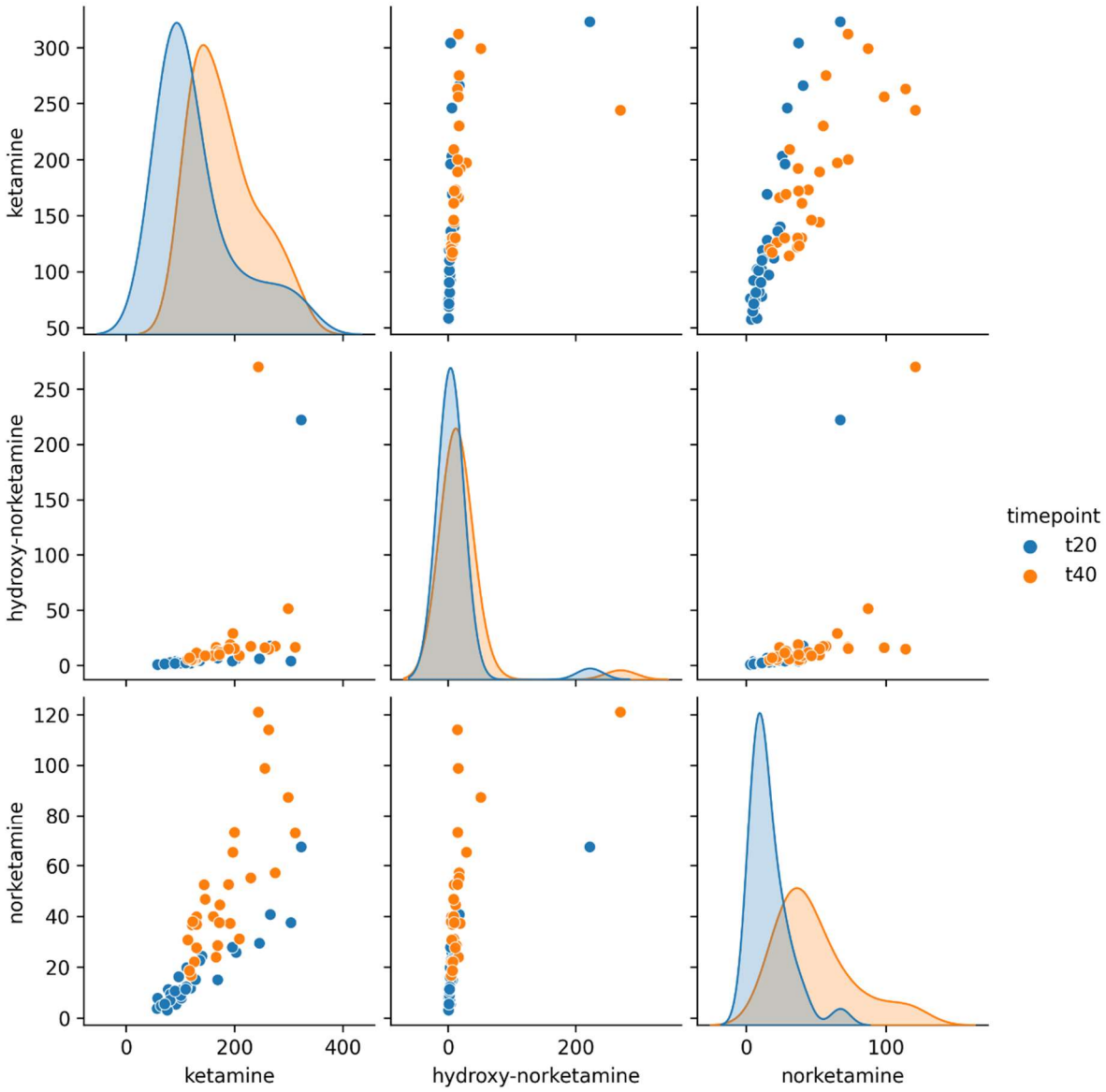


Figure 35: Paired plot comparisons of plasma concentrations of ketamine and its metabolites 20 and 40 mins after the beginning of the infusion. Each row illustrates the relationship between one of the metabolites and the two others. The top row corresponds to ketamine, the middle row to hydroxy-norketamine, the bottom row to norketamine. Data corresponding to the 20 mins after infusion starts time point are presented in blue. The one corresponding to the 40 mins after infusion starts time point are presented in orange. Units are ng/mL. Data falling outside of the 10 to 90% quantiles were excluded.

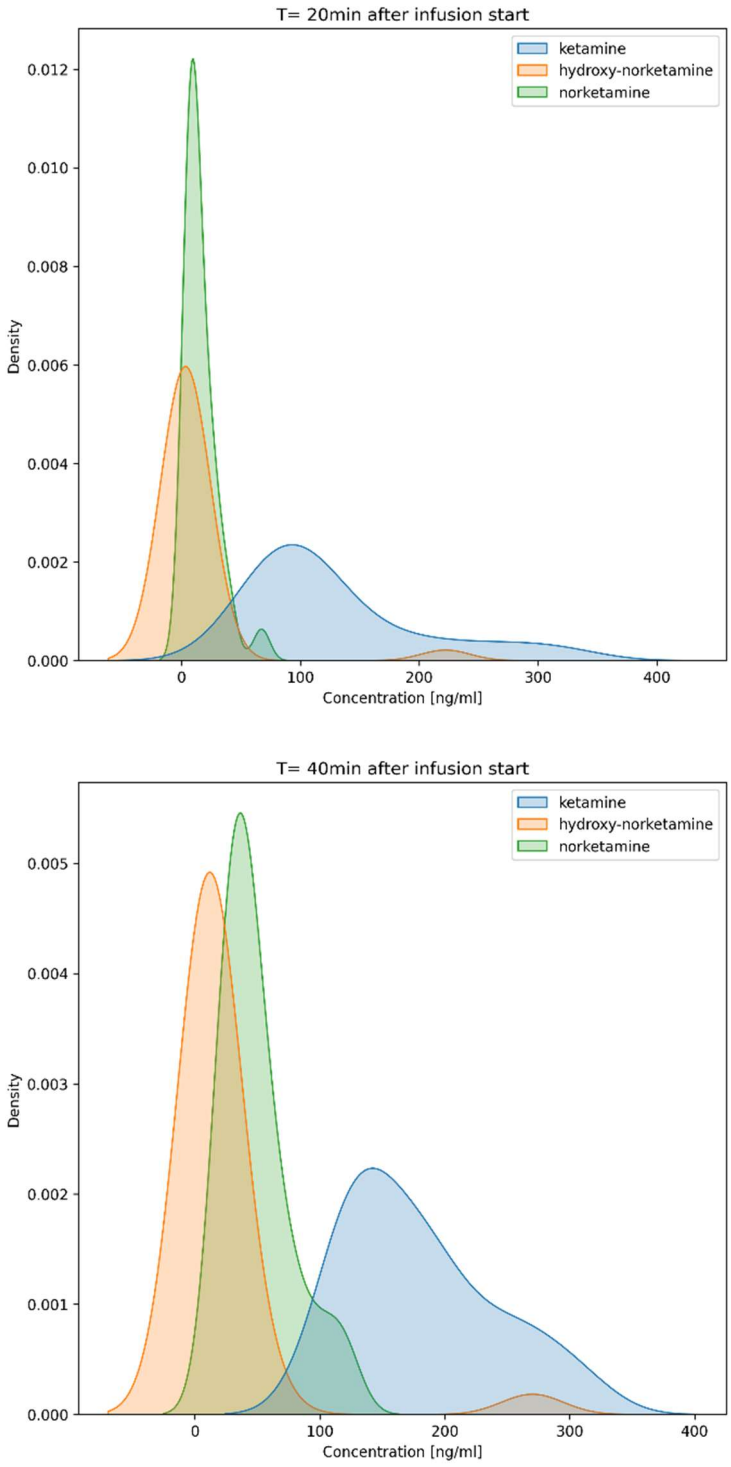


Figure 36: Distribution of the plasma concentration of ketamine and its metabolites 20 and 40 mins after the beginning of the infusion. Top panel: Concentration at T= 20 mins after the beginning of the infusion. Bottom panel: Concentration at T= 40 mins after the beginning of the infusion. The blue curve corresponds to ketamine, the orange curve to hydroxy-norketamine and the green curve to nortketamine. Data falling outside of the 10 to 90% quantiles were excluded.

4.3.5 Behavioural Analyses

4.3.5.1 Gamified Oddball – Reaction time

The LME model to analyse RT in the gamified Oddball task collected in the laboratory around the infusions contained 179 observations. There was a significant effect of session 1h after the infusions on RT in the gamified Oddball with an average estimated increase of 11.3ms (SE=5.5, $p<0.041$, $df_{residuals} = 173$). I also observed a fixed effect of drug during the session 1h before the infusion, with an estimated average increased RT in the ketamine condition of 12.4ms (SE=5.6, $p<0.027$, $df_{residuals} = 173$).

The LME model to analyse RT in the gamified Oddball task collected in the home during the week after the infusions contained 318 observations. No significant effect of session and/or drug were found (all p>009). All results are presented in Table 16 and on Figures 37 and 38.

In-laboratory analyses					
Reaction time during the gamified visual Oddball	**Coef. (SE)**	**z-stat**	**P-values**	**95% Confidence Interval**	**$df_{residuals}$**
Intercept	303.4 (6.2)	49.2	0.000	[291.3, 315.5]	173
Fixed Effect of drug at the 1hr before infusion session	12.4 (5.6)	2.2	0.027	[1.4, 23.3]	173
Fixed Effect of the 1hr after infusion session	11.3 (5.5)	2.0	0.041	[0.5, 22.1]	173
Fixed Effect of the 24hrs after infusion session	0.4 (5.5)	0.1	0.946	[10.5, 11.2]	173
Interaction between Drug and the 1hr after infusion session	-3.6 (7.9)	-0.5	0.642	[-19.0, 11.7]	173
Interaction between Drug and the 24hrs after infusion session	-13.1 (7.9)	-1.7	0.094	[-28.5, 2.3]	173
At home analyses					
Intercept	309.0 (7.5)	41.2	0.000	[294.3, 323.7]	314
Fixed Effect of Drug	2.5 (7.6)	0.3	0.742	[-12.3, 17.3]	314
Continuous fixed effect of session	0.0 (1.4)	0.0	0.981	[-2.7, 2.6]	314
Interaction between drug and sessions	0.1 (1.9)	0.1	0.949	[-3.7, 3.9]	314

Table 16: Linear mixed effect model estimates and Wald tests of the Reaction time during the gamified visual Oddball. Estimates of the fixed and random effects with their corresponding standard error (SE) and statistics of the individual estimates are provided.

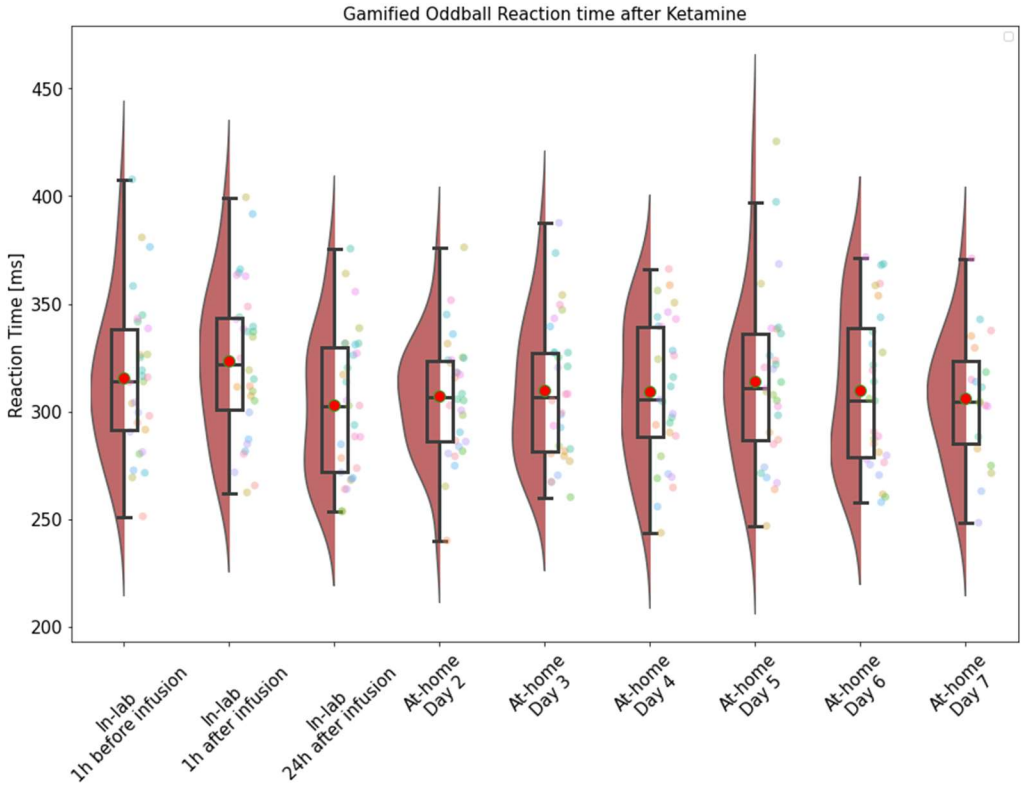


Figure 37: Reaction time to Target trials in the gamified Oddball across days after the ketamine infusion.

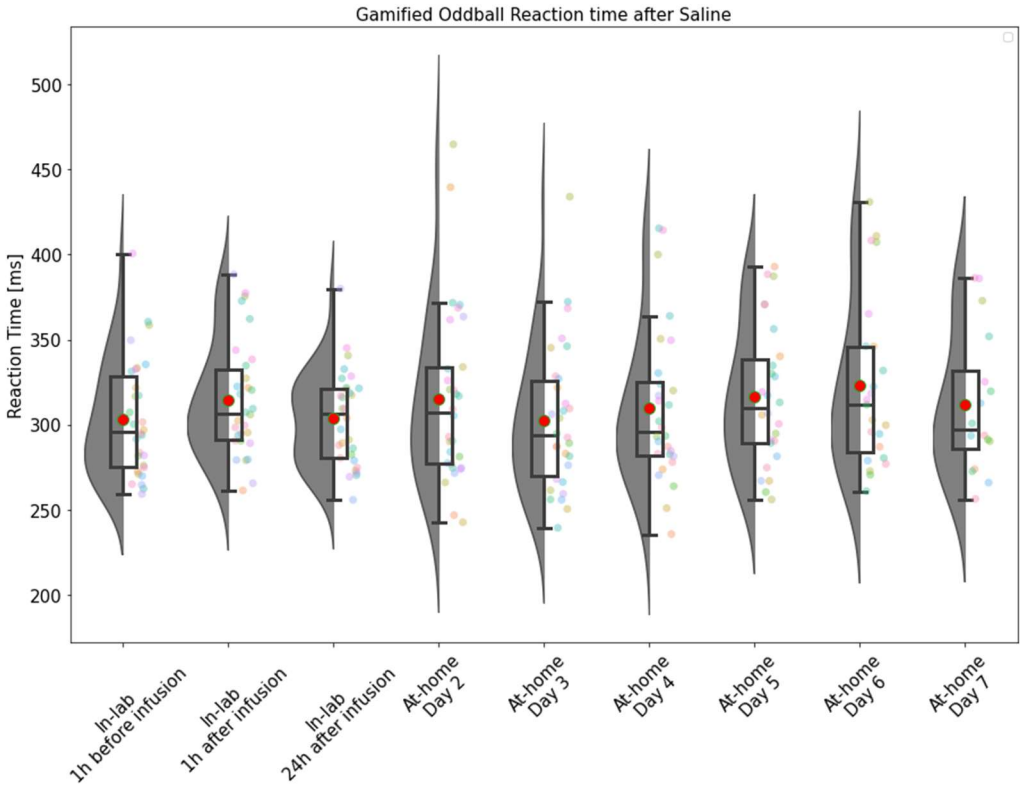


Figure 38: Reaction time to Target trials in the gamified Oddball across days after the saline infusion.

4.3.5.2 Gamified Flanker task – Reaction time successful trials

The LME model to analyse RT to all successful trials in the gamified Flanker task collected in the home during the week after the infusions contained 179 observations. No significant effect of session and/or drug was found (all $p>0.28$).

The LME model to analyse RT to all successful trials in the gamified Flanker task collected in the home during the week after the infusions contained 319 observations. No significant effect of session and/or drug was found (all $p>0.08$).

All results are presented in Table 17 and on Figures 39 and 40.

In-laboratory analyses					
Reaction time during the Flanker task to all successful trials	Coef. (SE)	z-stat	P-values	95% Confidence Interval	$df_{residuals}$
Intercept	306.0 (6.0)	51.4	0.000	[294.3, 317.6]	173
Fixed Effect of drug	6.3 (5.9)	1.1	0.288	[-5.3, 17.8]	173
Fixed Effect of the 1hr after infusion session	5.4 (5.8)	0.9	0.359	[-6.1, 16.8]	173
Fixed Effect of the 24hr after infusion session	-5.8 (5.8)	-1.0	0.319	[-17.2, 5.6]	173
Interaction between Drug and the 1hr after infusion session	1.1 (8.3)	0.1	0.898	[-15.2, 17.3]	173
Interaction between Drug and the 24hr after infusion session	-6.2 (8.3)	-0.7	0.456	[-22.4, 10.1]	173
At home analyses					
Intercept	302.2 (6.1)	49.5	0	[290.2, 314.1]	315
Fixed Effect of Drug	1.8 (5.5)	0.3	0.741	[-9.0, 12.7]	315
Continuous fixed effect of session	-0.1 (1.0)	-0.1	0.924	[-2.0, 1.8]	315
Interaction between drug and sessions	-2.5 (1.4)	-1.7	0.084	[-5.2, 0.3]	315

Table 17: Linear mixed effect model estimates and Wald tests of the Reaction time during the gamified Flanker task to all successful trials. Estimates of the fixed and random effects with their corresponding standard error (SE) and statistics of the individual estimates are provided.

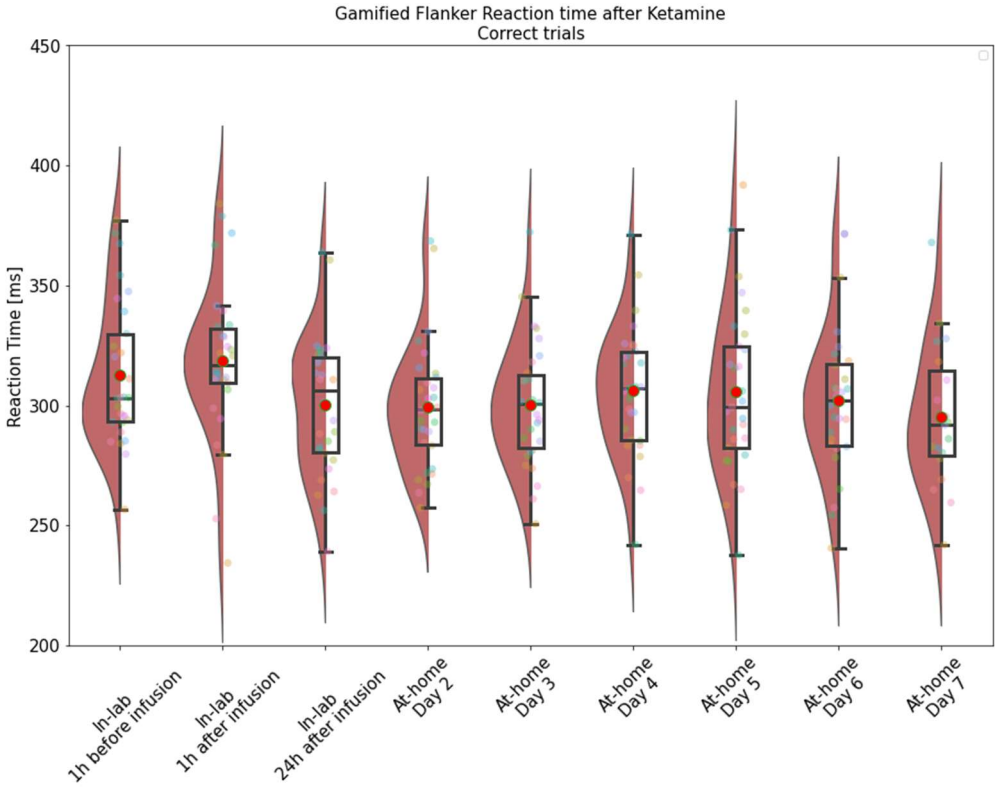


Figure 39: Reaction time to Correct trials in the gamified Flanker across days after the ketamine infusion.

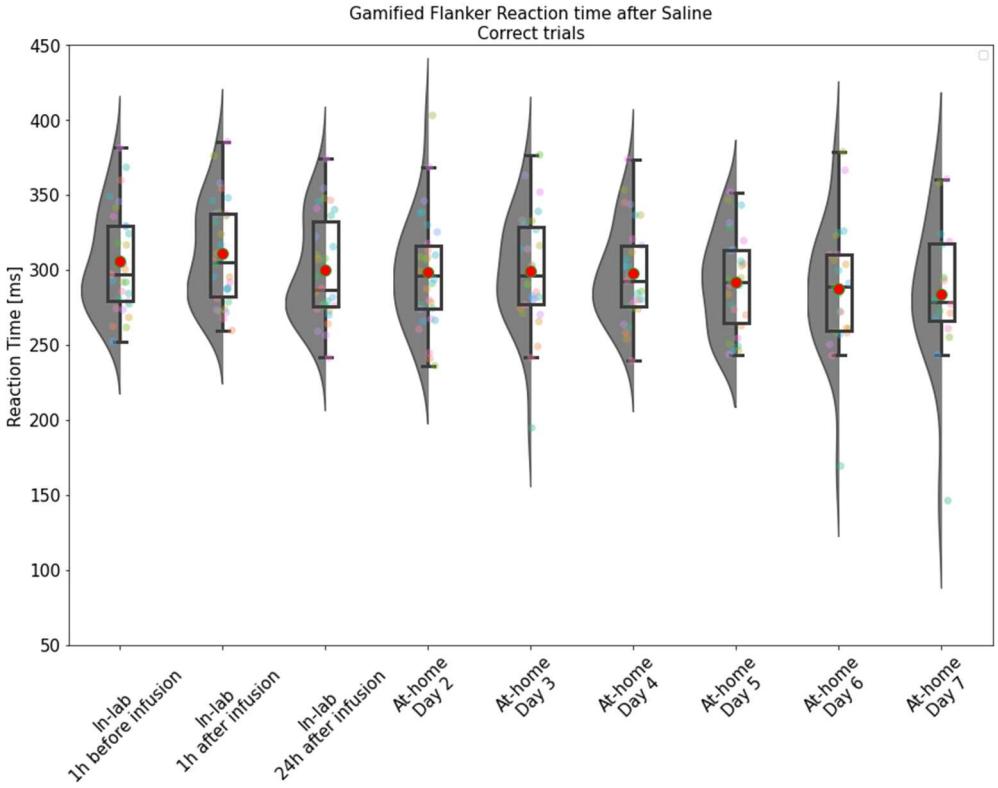


Figure 40: Reaction time to Correct trials in the gamified Flanker across days after the saline infusion.

4.3.5.3 Gamified Flanker task – Difference of Reaction times between incongruent minus congruent trials

The LME model to analyse difference of RT between incongruent minus congruent in the gamified Flanker task collected in the home during the week after the infusions contained 179 observations. There was a significant effect of session 24h after the infusions on difference of RT between incongruent minus congruent trials in the gamified Flanker with an average estimated decrease of difference of 7.6ms (SE=3.4, $p<0.024$, $df_{residuals} = 173$).

The LME model to analyse difference of RT between incongruent minus congruent in the gamified Flanker task collected in the home during the week after the infusions contained 319 observations. No significant effect of session and/or drug was found (all $p>0.2$). Results are presented in Table 18, and on Figures 41 and 42.

In-laboratory analyses					
	Coef. (SE)	**z-stat**	**P-values**	**95% Confidence Interval**	**$df_{residuals}$**
Intercept	36.6 (3.1)	11.9	0.000	[30.6, 42.6]	173
Fixed Effect of drug	2.7 (3.4)	0.8	0.434	[-4.0, 9.3]	173
Fixed Effect of the 1hr after infusion session	2.8 (3.4)	0.8	0.405	[-3.8, 9.4]	173
Fixed Effect of the 24hr after infusion session	-7.6 (3.4)	-2.3	0.024	[-14.2, -1.0]	173
Interaction between Drug and the 1hr after infusion session	7.6 (4.8)	1.6	0.11	[-1.7, 17.0]	173
Interaction between Drug and the 24hr after infusion session	5.2 (4.8)	1.1	0.276	[-4.2, 14.6]	173
At home analyses					
Intercept	37.6 (3.6)	10.4	0.000	[30.5, 44.6]	262
Fixed Effect of Drug	-5.7 (4.6)	-1.2	0.214	[-14.6, 3.3]	262
Continuous fixed effect of session	-0.4 (1.0)	-0.4	0.664	[-2.3, 1.5]	262
Interaction between drug and sessions	0.4 (1.4)	0.3	0.748	[-2.3, 3.2]	262

Table 18: Linear mixed effect model estimates and Wald tests of difference of reaction time between incongruent minus congruent trials in the Gamified Flanker Task. Estimates of the fixed and random effects with their corresponding standard error (SE) and statistics of the individual estimates are provided.

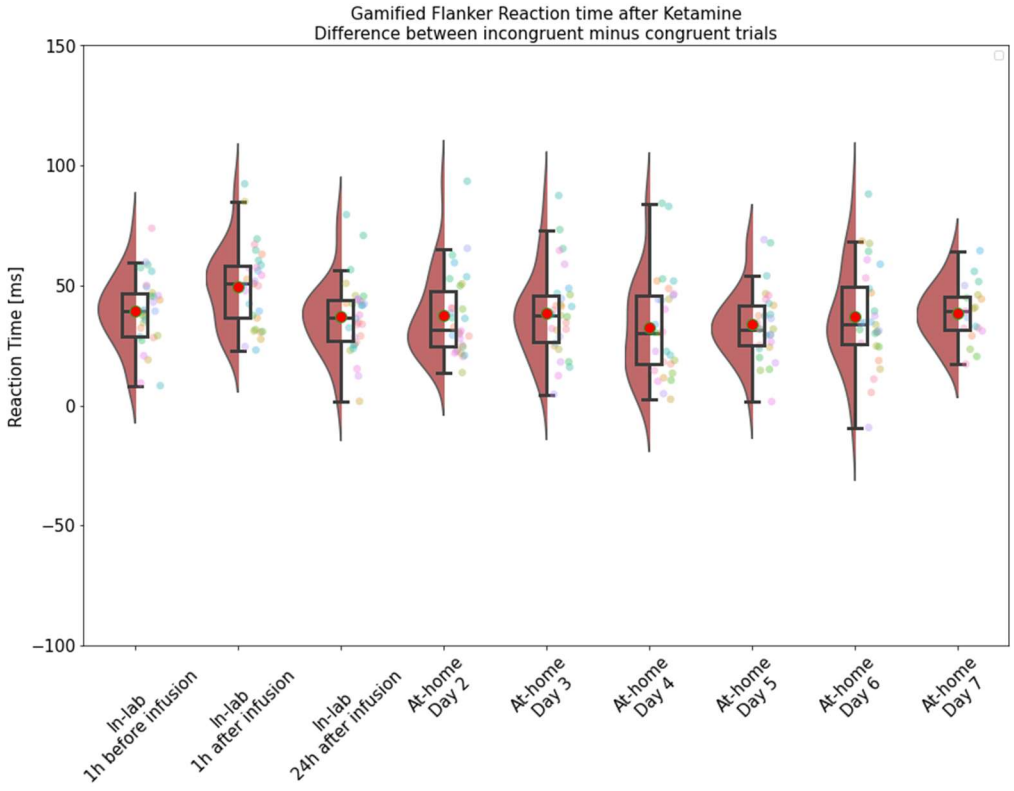


Figure 41: Difference of reaction time between incongruent minus congruent trials in the Gamified Flanker Task across days after the ketamine infusion.

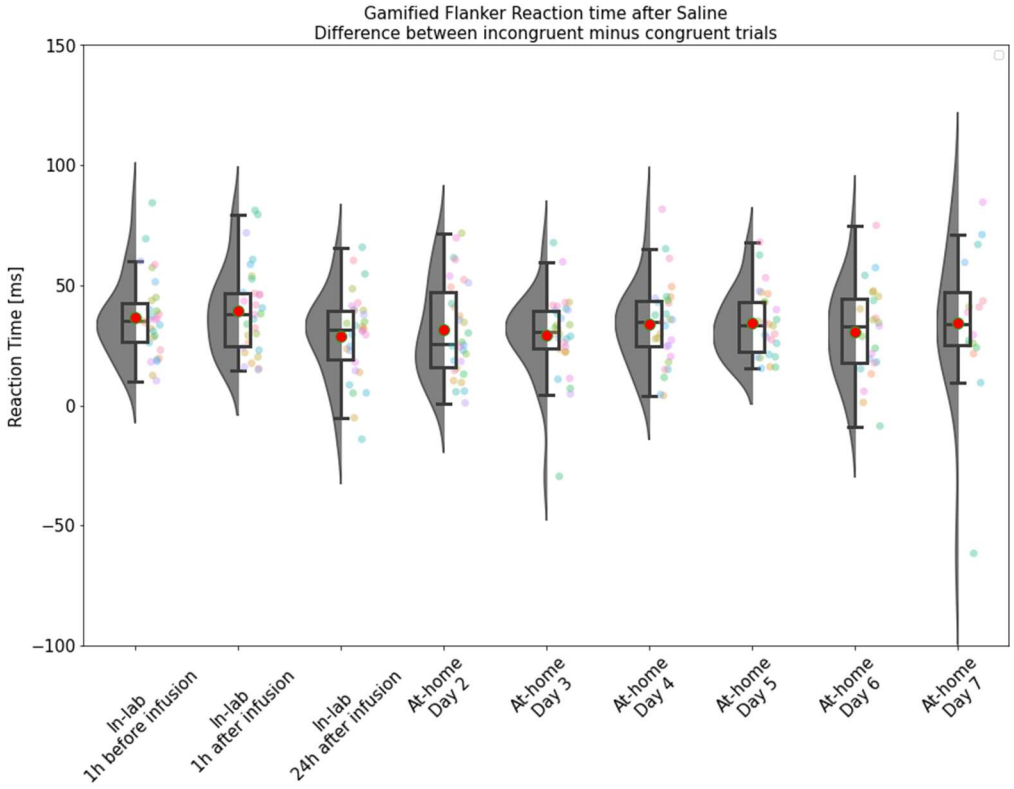


Figure 42: Difference of reaction time between incongruent minus congruent trials in the Gamified Flanker Task across days after the saline infusion.

		Gamified Oddball	Gamified Flanker	Gamified Flanker
	Session	Reaction Time (SE) [ms]	Reaction Time Correct trial (SE) [ms]	Difference in RT Between incongruent minus congruent trials (SE)[ms]
Ketamine	1h before infusion	315.6 (6.7)	312.8 (5.6)	39.2 (2.8)
	1h after infusion	323.4 (6.6)	318.6 (5.9)	49.7 (3.1)
	24h after infusion	303.0 (6.1)	300.2 (5.3)	36.9 (2.9)
	Day 2 after infusion	308.8 (5.7)	298.2 (5.5)	38.4 (3.6)
	Day 3 after infusion	309.5 (6.4)	300.7 (4.9)	40.6 (3.2)
	Day 4 after infusion	311.0 (6.0)	306.0 (5.4)	32.7 (4.0)
	Day 5 after infusion	311.4 (6.7)	304.9 (6.5)	31.8 (2.6)
	Day 6 after infusion	310.9 (7.5)	302.9 (5.9)	40.5 (3.6)
	Day 7 after infusion	305.5 (6.3)	298.1 (5.2)	32.8 (3.1)
Saline	1h before infusion	303.4 (6.4)	306.0 (6.2)	36.6 (3.1)
	1h after infusion	314.7 (6.2)	311.3 (6.3)	39.4 (3.3)
	24h after infusion	303.7 (5.1)	300.1 (6.3)	29.0 (3.3)
	Day 2 after infusion	316.0 (11.0)	300.1 (7.8)	34.1 (3.8)
	Day 3 after infusion	310.6 (8.2)	295.7 (7.5)	28.2 (3.7)
	Day 4 after infusion	304.1 (8.6)	298.1 (6.5)	33.8 (3.5)
	Day 5 after infusion	319.9 (9.0)	294.8 (6.5)	32.6 (3.0)
	Day 6 after infusion	316.5 (9.6)	289.0 (8.7)	31.3 (3.6)
	Day 7 after infusion	310.4 (8.5)	288.7 (8.9)	33.0 (5.6)

Table 19: Summary table of all behavioural metrics broken down per day across all subjects.

4.3.6 EEG Analyses

4.3.6.1 Eyes-Closed Resting State Task and Band Power Analysis

Before investigating differences between the ketamine and saline conditions, I first assessed the integrity of the recordings by observing that all recordings exhibited the typical features expected in human EEG Power Spectral Density (PSD). Specifically, I observed: a spectral power decay with increasing frequencies and an alpha peak between 8 to 12 Hz.

When examining the recordings performed during each infusion (Figure 43) and the corresponding T-values (Figure 44), increases in gamma band power were noticeable. One-sided paired t-tests revealed significant increase at electrode Fz in normalized power in the ketamine compared to the saline condition across one larger cluster ranging from frequencies 24.3 to 40 Hz (df = 29, p-value = 6.19x10E-12). At electrode FCz, similar increases in the ketamine compared to the saline condition were observed in three smaller clusters ranging from frequencies 32.3 to 40 Hz (df = 29, p-values < 0.024). I did not observe the expected disruption in the alpha band (Figure 43). No significant effect of time and/or drug were found when examining the sessions collected after the infusions either in the laboratory or collected from the home (all p-values > 0.05).

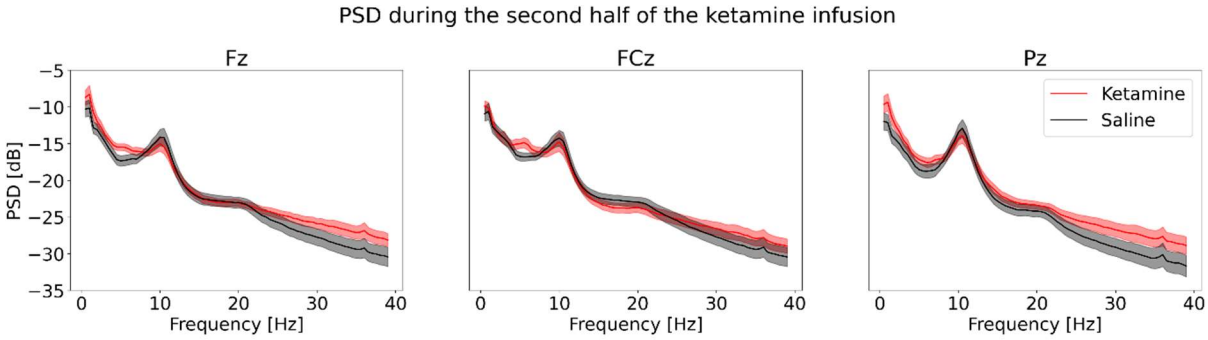


Figure 43: Resting State Power Spectral Density during the second half of the infusion. The red line corresponds to the ketamine condition. The black line corresponds to the saline condition. N = 30, n = 1 session per participant. Shaded areas represent a 95% confidence interval. From left to right: Fz, FCz, and Pz electrodes.

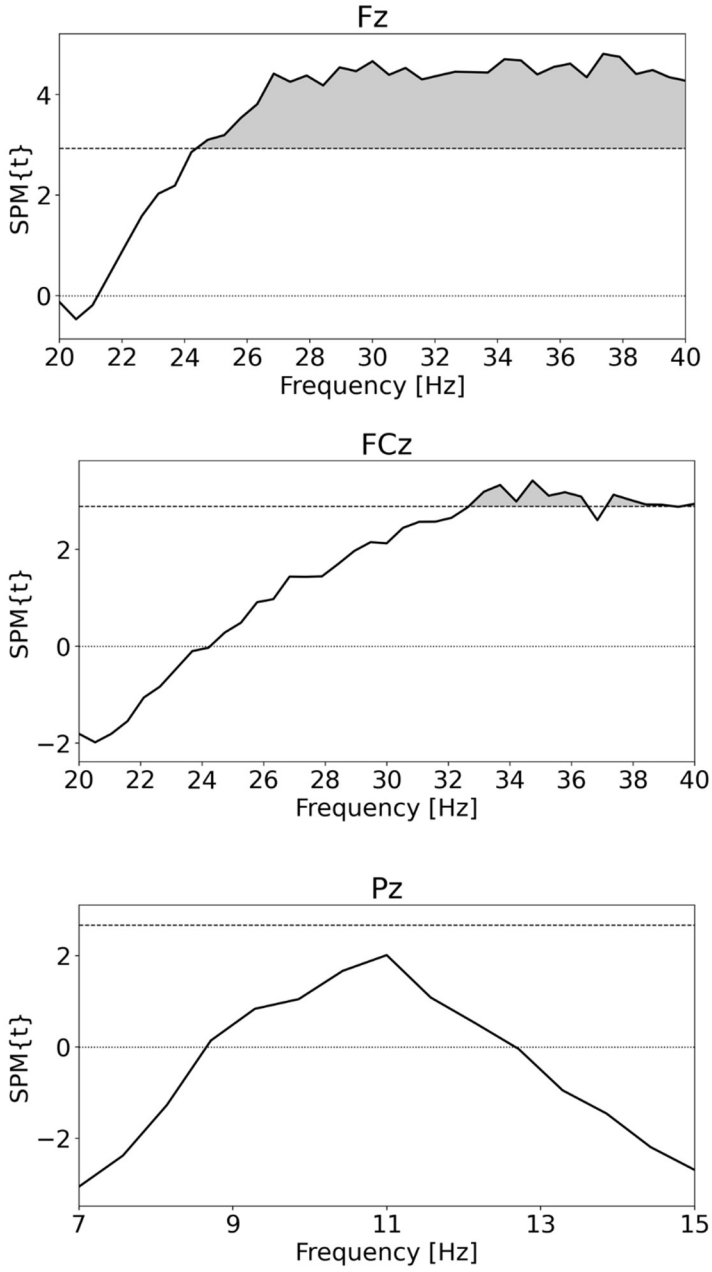


Figure 44: T-values extracted from the one-sided paired t-test statistical analyses of the power spectral density during the second half of the infusion. Top row: Fz electrodes, middle row: FCz electrode, bottom row: Pz electrodes. Analyses of the gamma frequency were conducted at electrodes Fz and FCz (e.g., from 20 to 40Hz). Analyses of the alpha frequency band was conducted at Pz (e.g., from 7 to 15Hz). Shaded areas represent where the t-values reached the critical t-values, that is where the two conditions where significantly different from one another. Analyses included 30 participants.

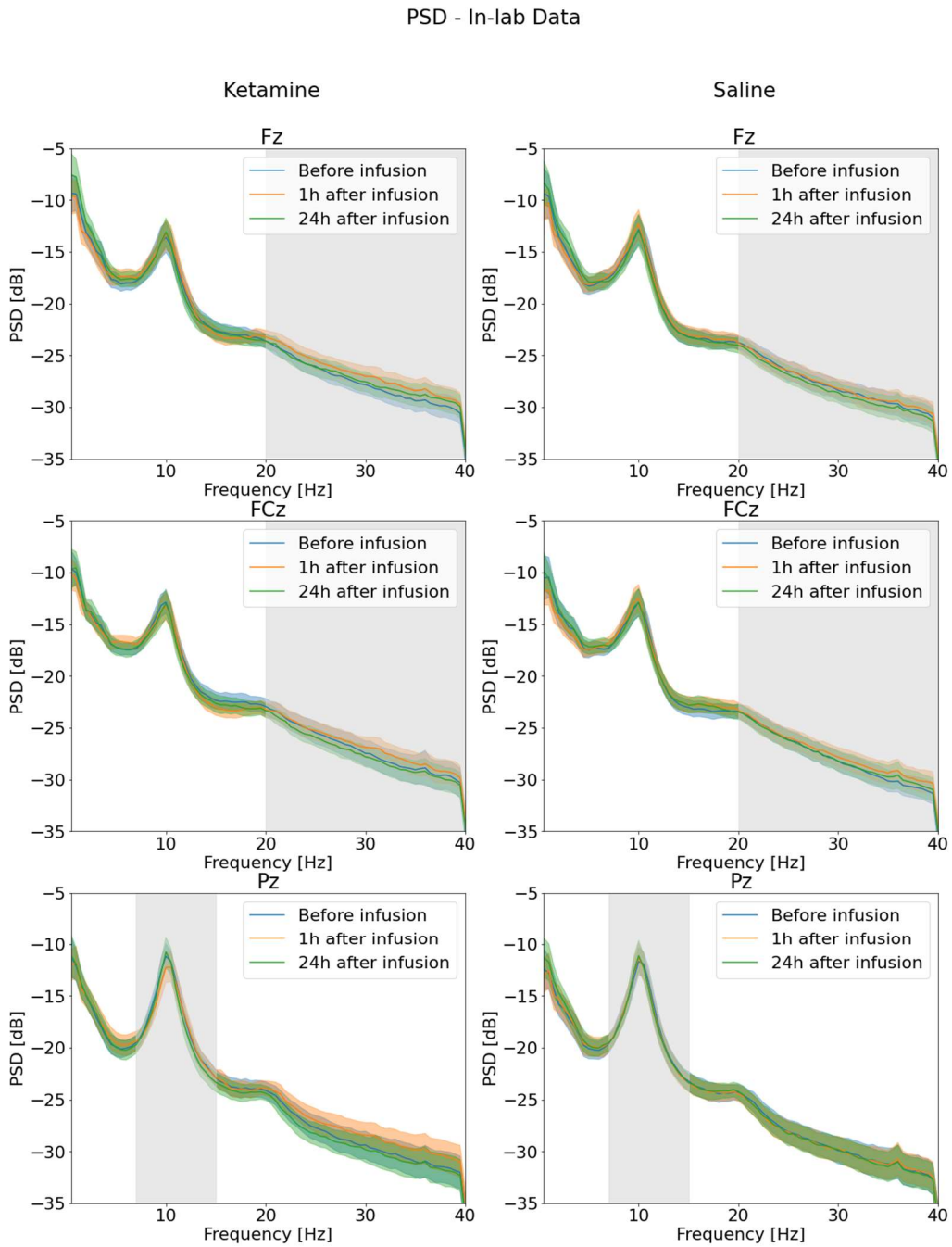


Figure 45: Resting State Power Spectral Density collected in the laboratory before, 1 hr after and 24 hrs after the infusions. The blue line corresponds to the 1 hr before infusion timepoint, the orange line to the 1 hr after infusion timepoint and the green line to the 24 hrs after infusion timepoint. The left column corresponds to the ketamine condition and the right column to the saline condition. N = 30, n = 1 session per participant. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the frequency bands across which the statistical analyses where conducted.

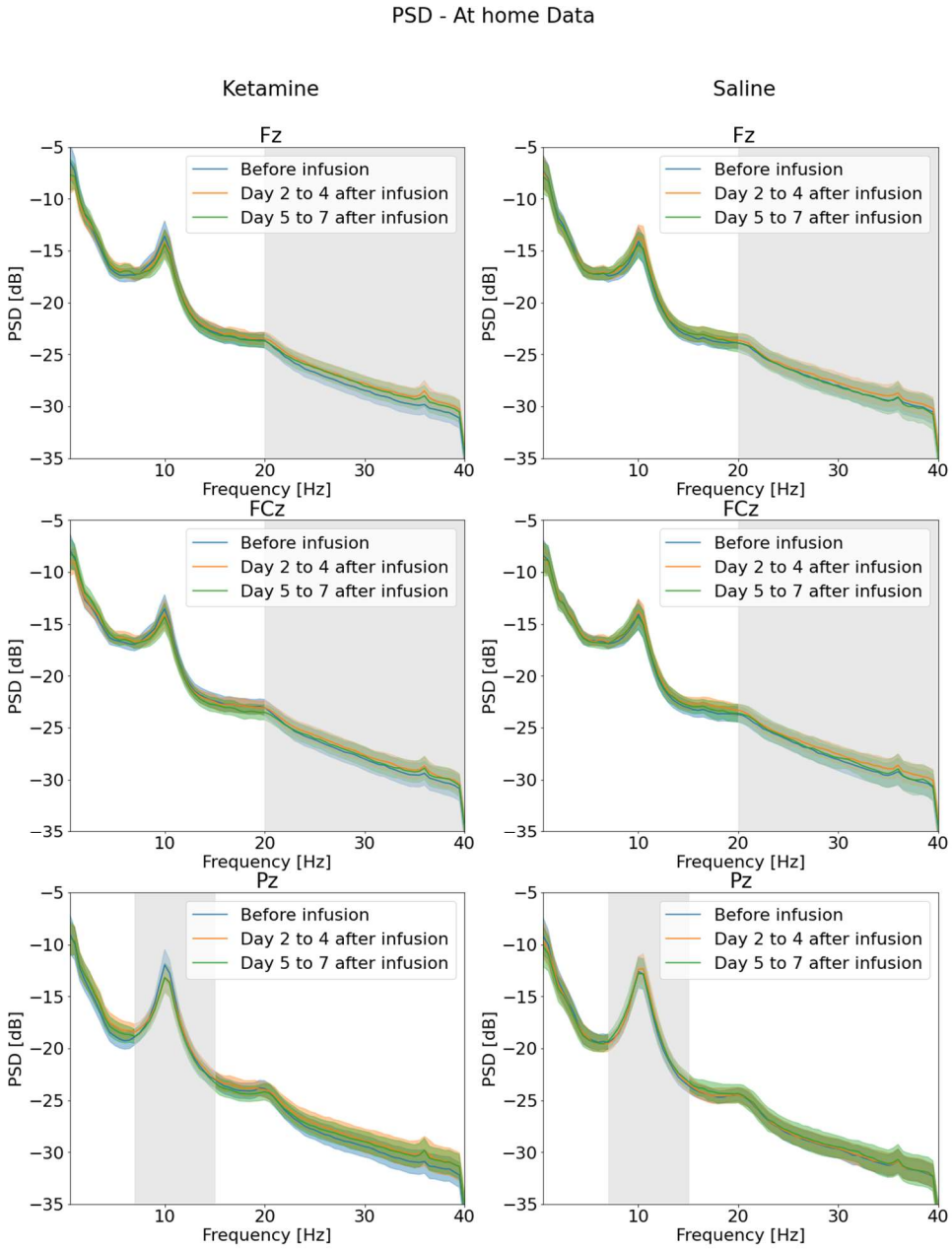


Figure 46: Resting State Power Spectral Density collected in the home during the week before, day 2 to 4 days after, and 5 to 7 days after the infusions. The blue line corresponds to data collected during the week before the infusion, the orange line to data collected during Day 2 to Day 4 after infusion, and the green line to data collected during Day 5 to Day 7 after infusion. The left column corresponds to the ketamine condition and the right column to the saline condition. N = 30, n ~= 3 session per participant. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the frequency bands across which the statistical analyses where conducted.

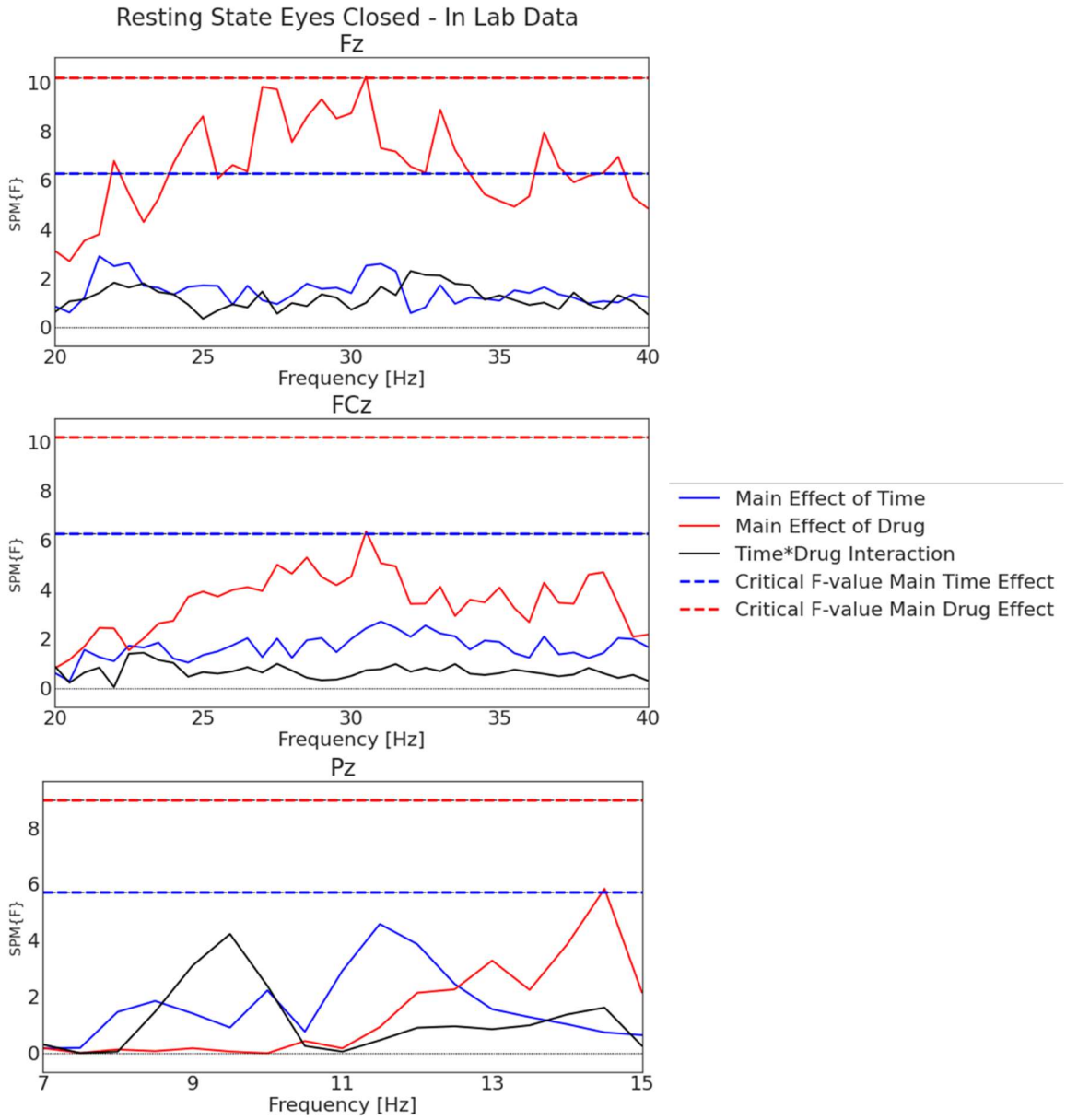


Figure 47: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the laboratory. Top row: Fz electrodes, middle row: FCz electrode, bottom row: Pz electrodes. Analyses of the gamma frequency were conducted at electrodes Fz and FCz (e.g., from 20 to 40Hz). Analyses of the alpha frequency band was conducted at Pz (e.g., from 7 to 15Hz). Shaded areas represent where the F-values reached the critical F-values, that is where the two conditions where significantly different from one another. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes Fz, FCz, and Pz included 30, 30 and 29 participants, respectively.

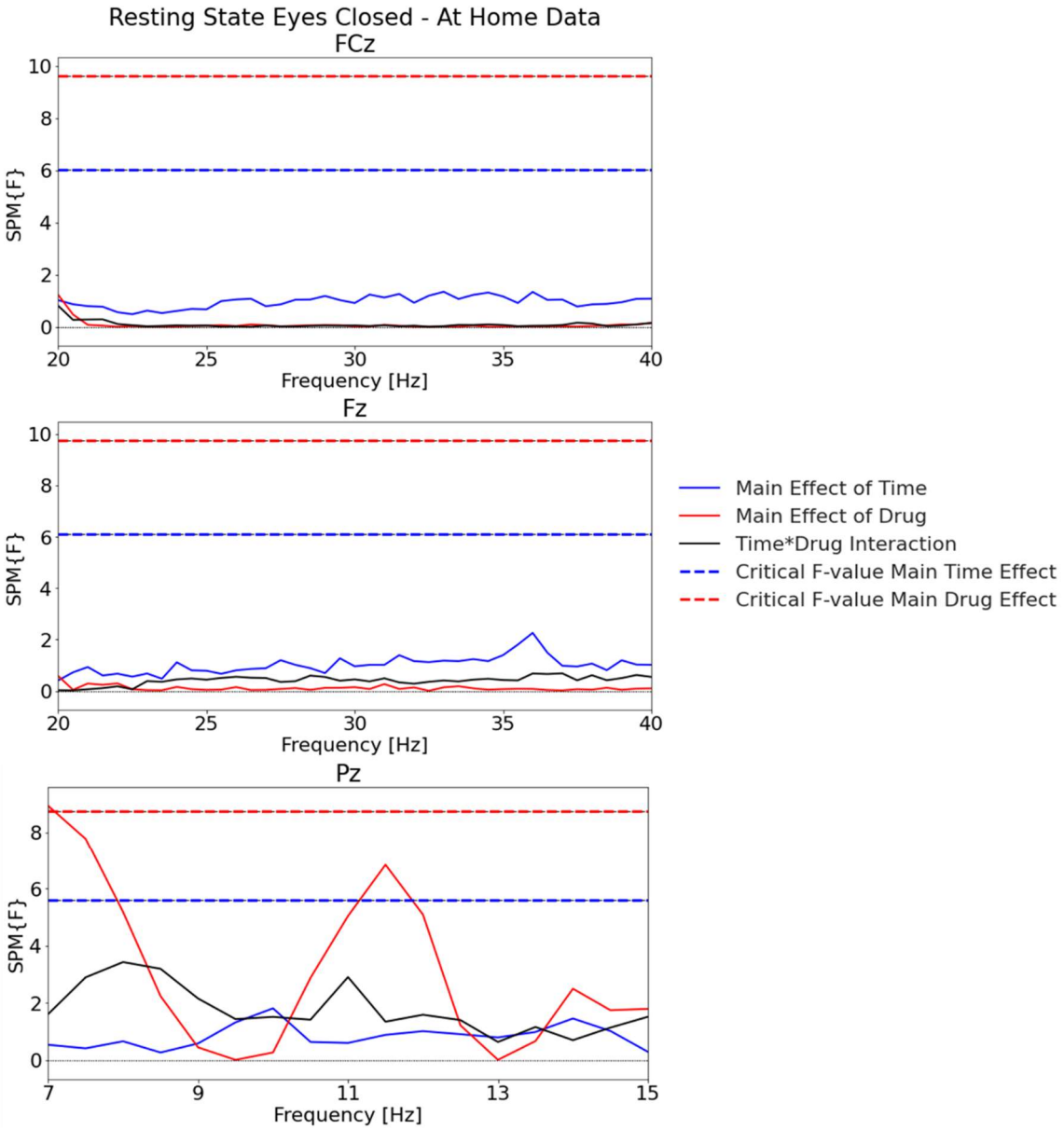


Figure 48: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the home. Top row: Fz electrodes, middle row: FCz electrode, bottom row: Pz electrodes. Analyses of the gamma frequency were conducted at electrodes Fz and FCz (e.g., from 20 to 40Hz). Analyses of the alpha frequency band was conducted at Pz (e.g., from 7 to 15Hz). Shaded areas represent where the t-values reached the critical t-values, that is where the two conditions where significantly different from one another. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes FCz, Fz, and Pz included 30 participants.

4.3.6.2 Passive Auditory Oddball and The Mismatch Negativity (MMN)

Firstly, I note that the key features of the MMN can be observed at all timepoints: the signal is composed of a negative deflection between 100 to 200 ms followed by positive signal from 200 to 400 ms with a frontocentral distribution. The clinical literature suggests that the MMN should be disrupted (reduced in amplitude and delayed) during acute ketamine infusion. These effects are not observed here and neither the in-laboratory or at home repeated ANOVAs reached significance (all p-values > 0.05). Results are presented on Figures 49 to 52.

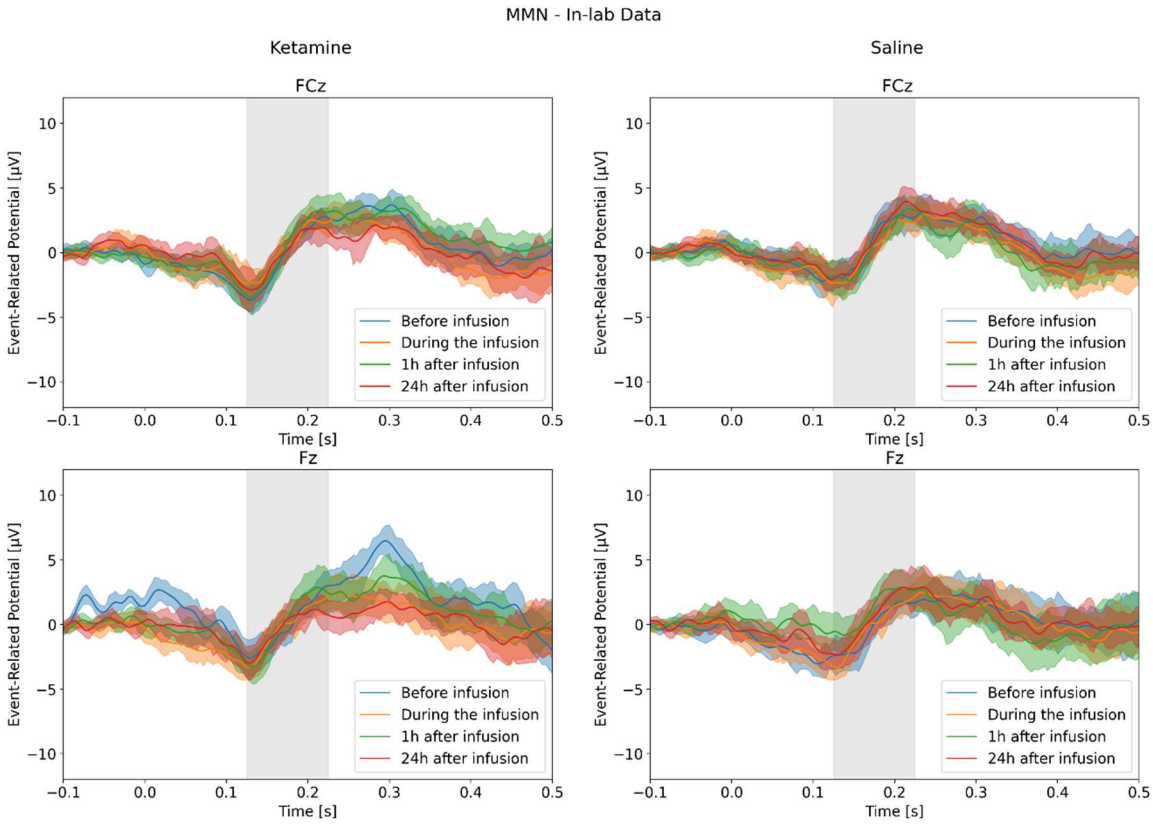


Figure 49: Mismatch Negativity Task before, during, 1h after, and 24h after each infusion. Data were collected in the laboratory under researchers' supervision. The blue line corresponds to the 1h before infusion timepoint, the orange line to the during infusion timepoint, the green line to the 1h after infusion timepoint, and finally the red line to the 24h after infusion timepoint. The left column corresponds to the ketamine condition and the right column to the saline condition. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the time window across which the statistical analyses where conducted.

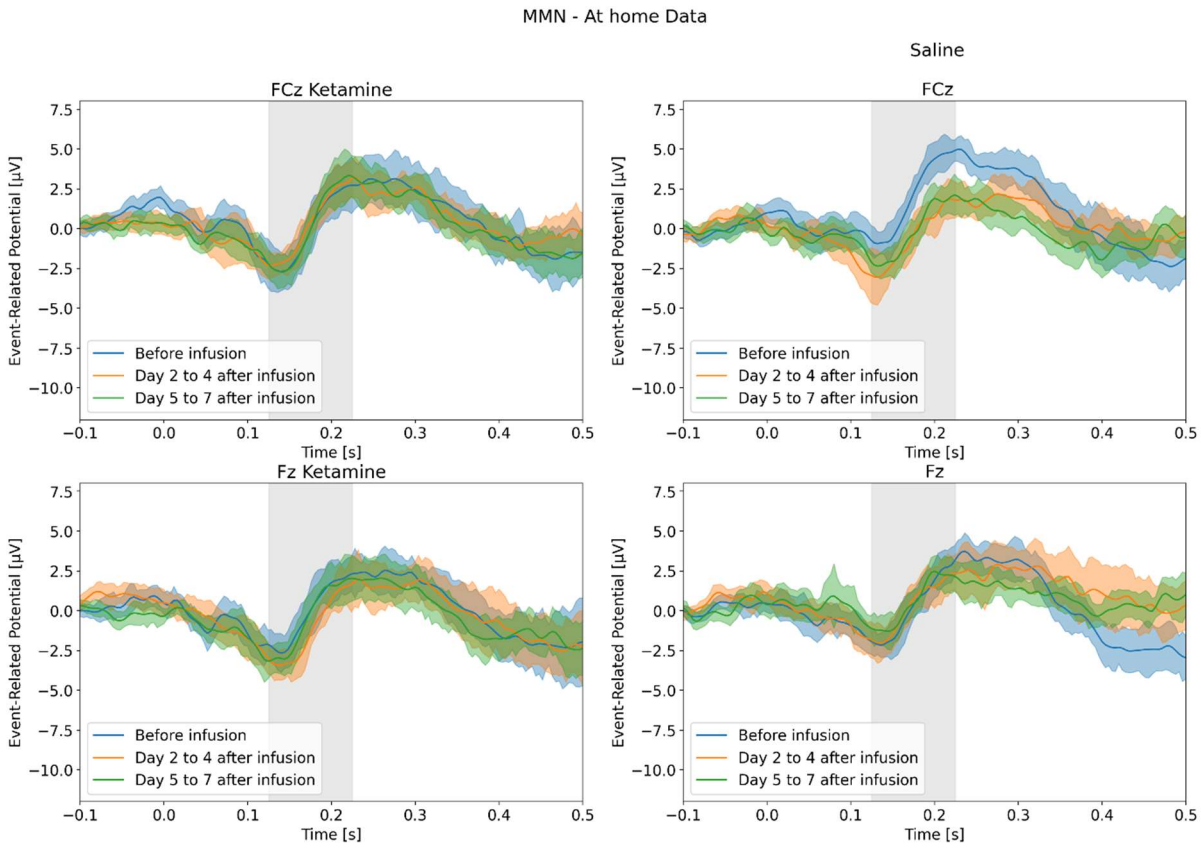


Figure 50: Mismatch Negativity Task during the week after the ketamine and saline infusions. Data were collected from the home. The blue line corresponds to data collected during the week before the infusion, the orange line to data collected during Day 2 to Day 4 after infusion, and the green line to data collected during Day 5 to Day 7 after infusion. The left column corresponds to the ketamine condition and the right column to the saline condition. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the time window across which the statistical analyses where conducted.

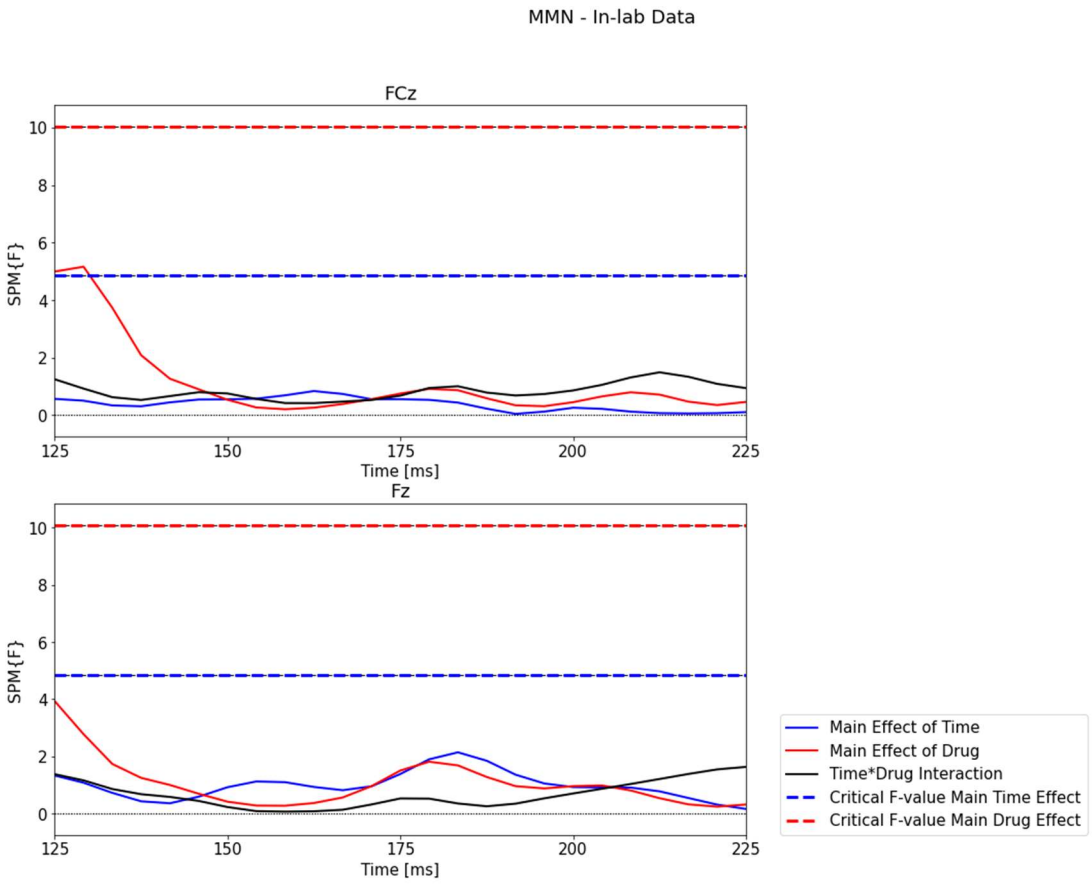


Figure 51: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the laboratory. Top row: FCz electrodes, bottom row: Fz electrode. Analyses of the mismatch negativity were conducted across the 125 to 225ms time-windows post-stimulus presentation. Shaded areas represent where the F-values reached the critical F-values. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes FCz and Fz included 29 and 26 participants, respectively.

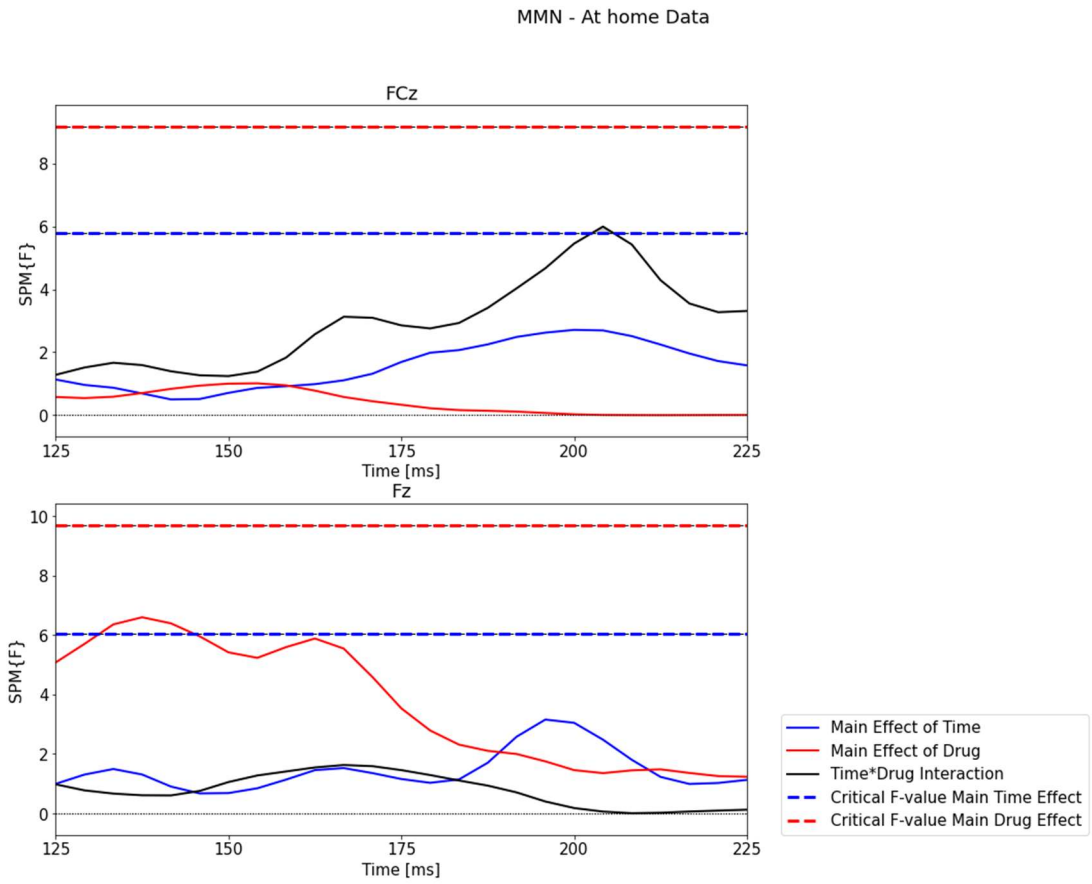


Figure 52: F-values extracted from the repeated Two-way ANOVAs conducted on data collected in the home. Top row: FCz electrodes, bottom row: Fz electrode. Analyses of the mismatch negativity were conducted across the 125 to 225 ms time-window post-stimulus presentation. Shaded areas represent where the F-values reached the critical F-values. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes FCz and Fz included 30 and 29 participants, respectively.

4.3.6.3 Gamified Visual 2-Stimulus Oddball and the P300

The analysis of the 2-stimulus Oddball paradigm was centred around 2 electrodes: Cz and Pz. Those electrodes were chosen as the P300 is typically reported in the literature to be the strongest in centro-parietal regions. Both in the in-laboratory and at home dataset, the expected signals are observed. First, early sensory processing components can be observed, followed by the P300 peaking around 350ms. When looking at the ANOVA results, no significant effects were found neither in the laboratory nor in the home datasets (all p-values > 0.05). Results are presented on Figures 53 to 56.

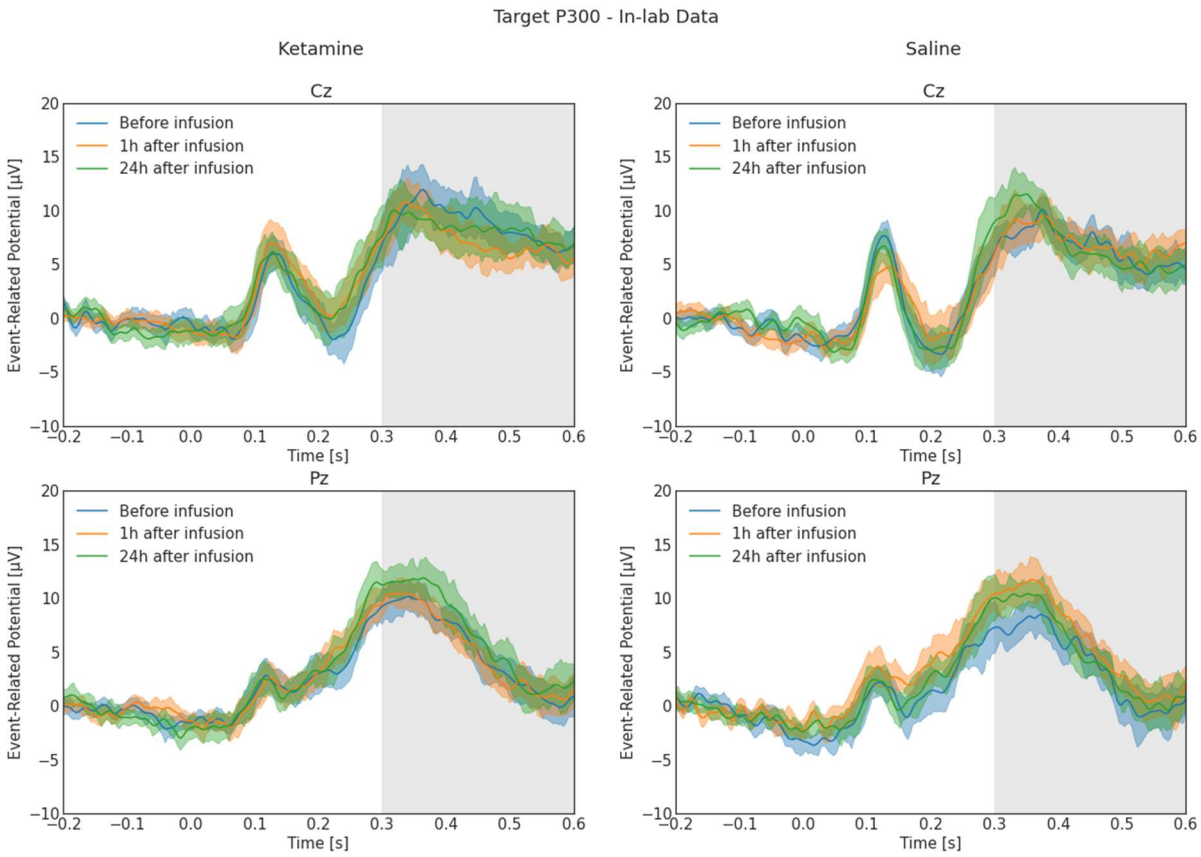


Figure 53: Grand average ERPs extracted from Astrotap locked to Target stimulus. Data were collected in the laboratory under researchers' supervision. The blue line corresponds to the 1h before infusion timepoint, the orange line to the 1h after infusion timepoint, and the green line to the 24 hrs after infusion timepoint. The left column corresponds to the ketamine condition and the right column to the saline condition. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the time window across which the statistical analyses where conducted.

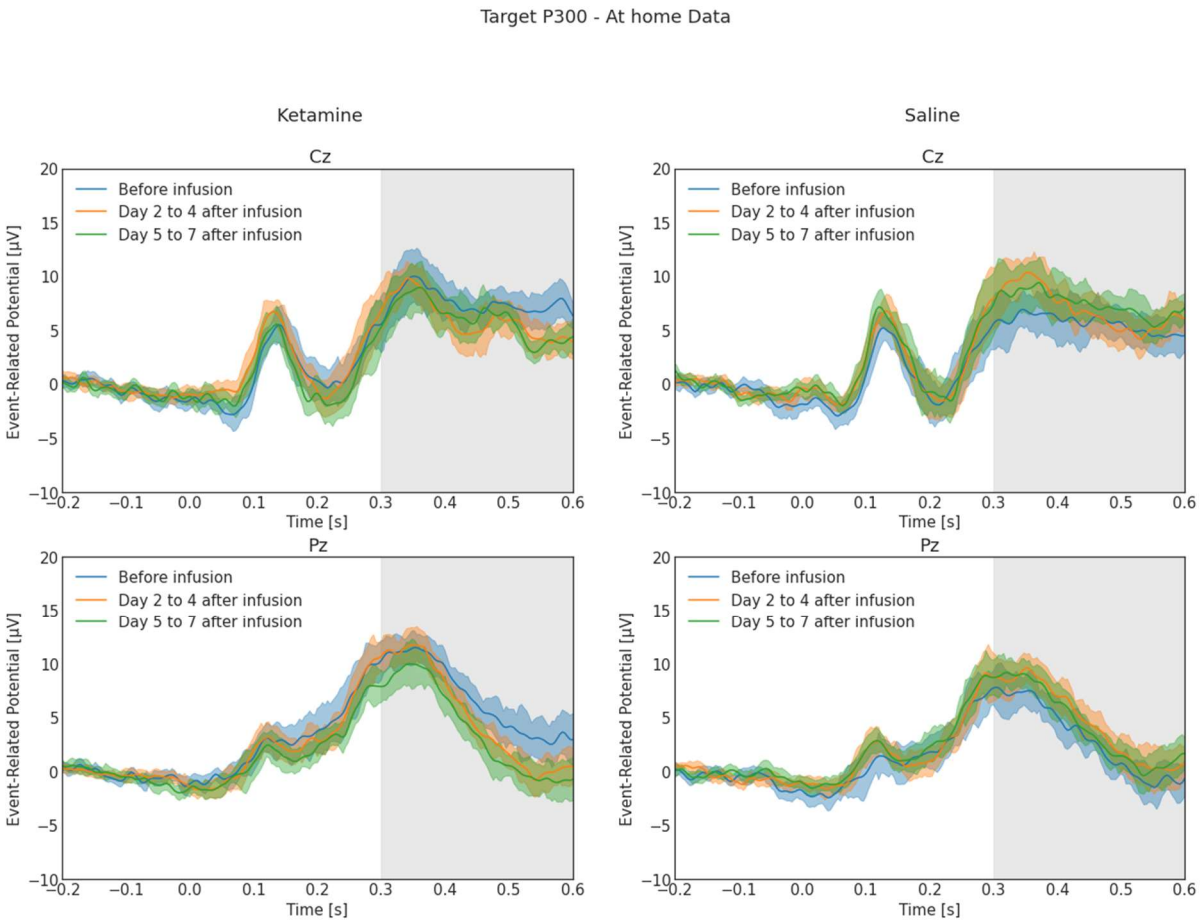


Figure 54: Grand average ERPs extracted from Astrotap locked to Target stimulus. Data were collected from the home. The blue line corresponds to data collected during the week before the infusion, the orange line to data collected during Day 2 to Day 4 after infusion, and the green line to data collected during Day 5 to Day 7 after infusion. The left column corresponds to the ketamine condition and the right column to the saline condition. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the time window across which the statistical analyses where conducted.

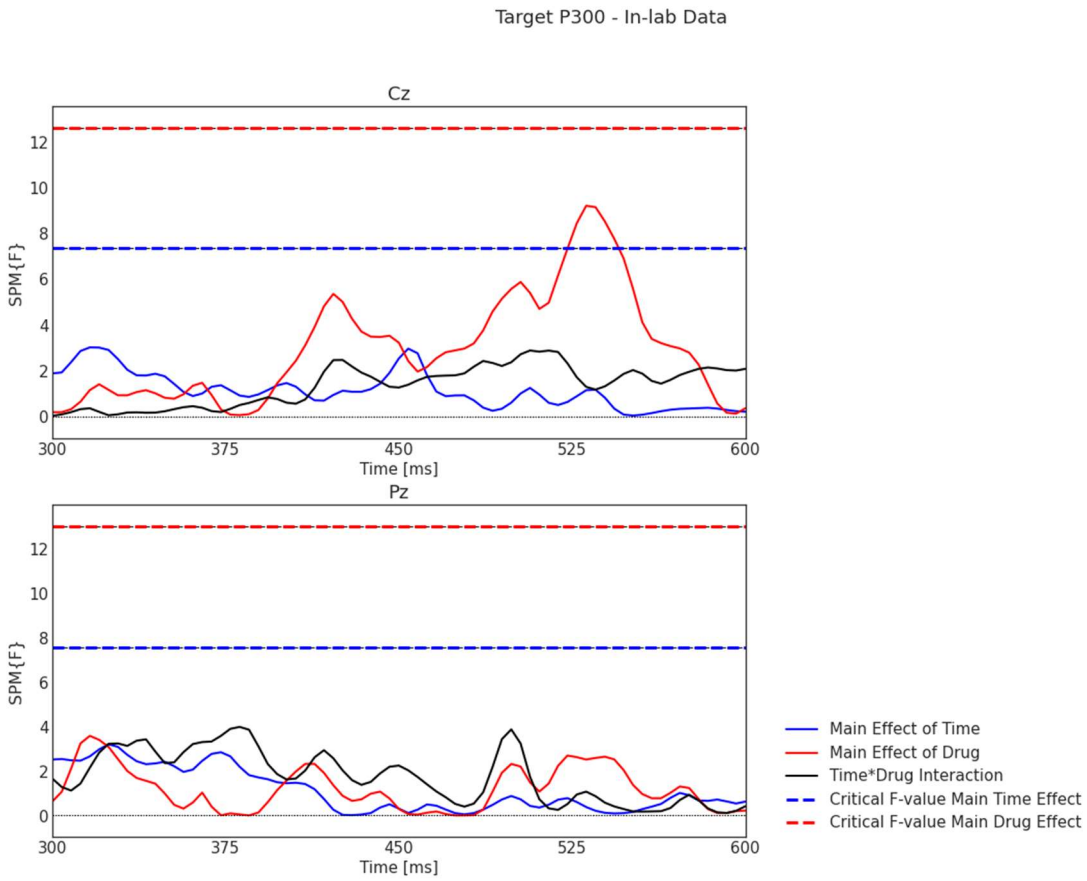


Figure 55: F-values extracted from the repeated Two-way ANOVAs conducted on Astrotap data collected in the laboratory. Top row: Cz electrodes, bottom row: Pz electrode. Analyses of the P300 were conducted across the 300 to 600 ms time-window post-stimulus presentation. blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes Cz and Pz included 25 and 27 participants, respectively.

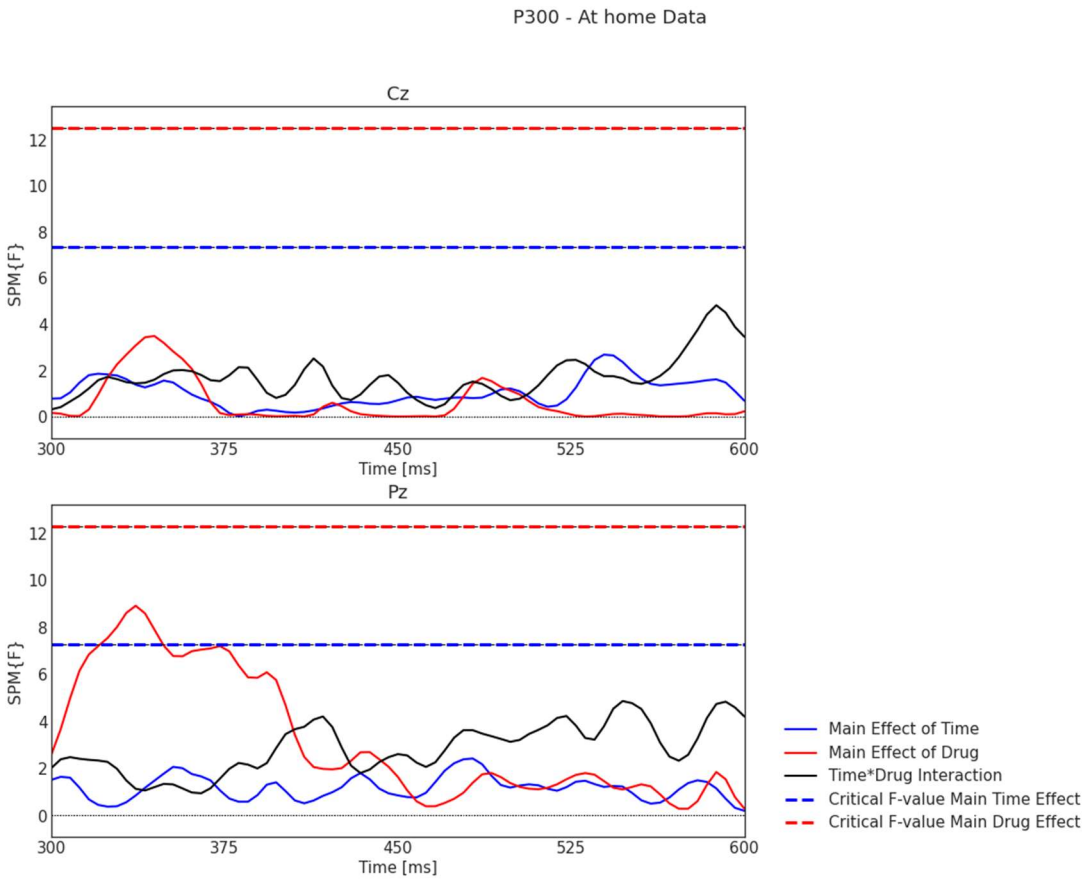


Figure 56: F-values extracted from the repeated Two-way ANOVAs conducted on astrotap data collected from the home. Top row: Cz electrodes, bottom row: Pz electrode. Analyses of the P300 were conducted across the 300 to 600 ms time-window post-stimulus presentation. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes Cz and Pz included 25 and 29 participants, respectively.

4.3.6.4 Gamified Adaptive Flanker Task and the Error-Related-Negativity (ERN)

The last set of analyses was focused on the gamified Flanker task. As before, I evaluated brain activity 1 hr, 24 hr and a week after infusion and compared at-home and in-laboratory data against their respective at-home or in-laboratory baselines. Data presented here differs from the rest of the dataset as the ERPs are locked to the participants' response rather than the presentation of the stimulus. As the ERN is generated in fronto-central areas, I focused my attention on the FCz and Cz electrodes. Results are presented on Figures 57 to 60. Before evaluating potential drug effects, I first noted the expected waveforms both in correct and incorrect trials. A clear ERN pattern could also be observed.

When looking at the ANOVA results, no significant effects were found neither in the laboratory nor in the home datasets (all p-values > 0.05). No significant effects were found in the home datasets. Analyses at electrodes Cz and FCz included 25 and 27 participants, respectively. Results are presented on Figures 57 to 60.

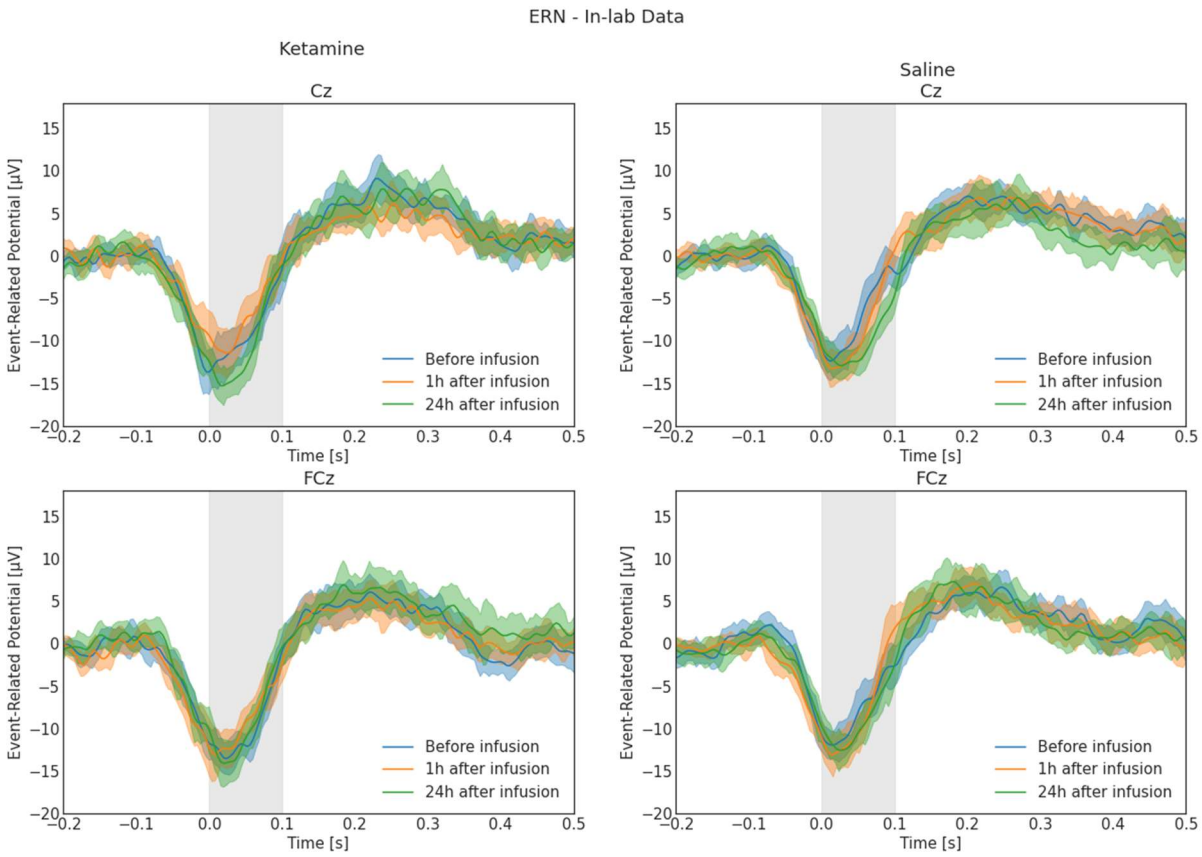


Figure 57: Grand average ERPs extracted from Go With The Flow locked to participants' responses. Data were collected in the laboratory under researchers' supervision. The blue line corresponds to the 1h before infusion timepoint, the orange line to the 1h after infusion timepoint, and the green line to the 24 hrs after infusion timepoint. The left column corresponds to the ketamine condition and the right column to the saline condition. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the time window across which the statistical analyses where conducted.

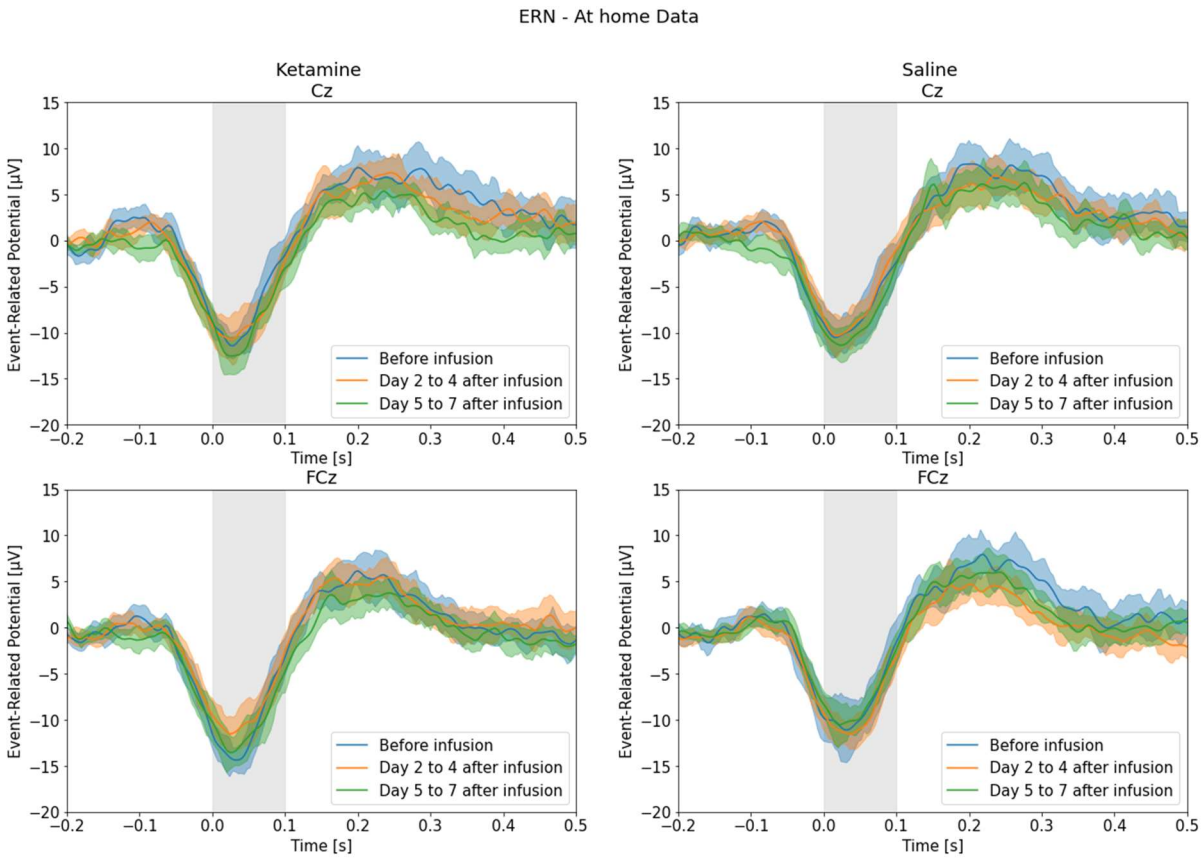


Figure 58: Grand average ERPs extracted from Go With The Flow locked to participants' responses. Data were collected from the home. The blue line corresponds to data collected during the week before the infusion, the orange line to data collected during Day 2 to Day 4 after infusion, and the green line to data collected during Day 5 to Day 7 after infusion. The left column corresponds to the ketamine condition and the right column to the saline condition. Coloured shaded areas represent the 95% confidence intervals of the corresponding signals. The grey vertical regions mark the time window across which the statistical analyses where conducted.

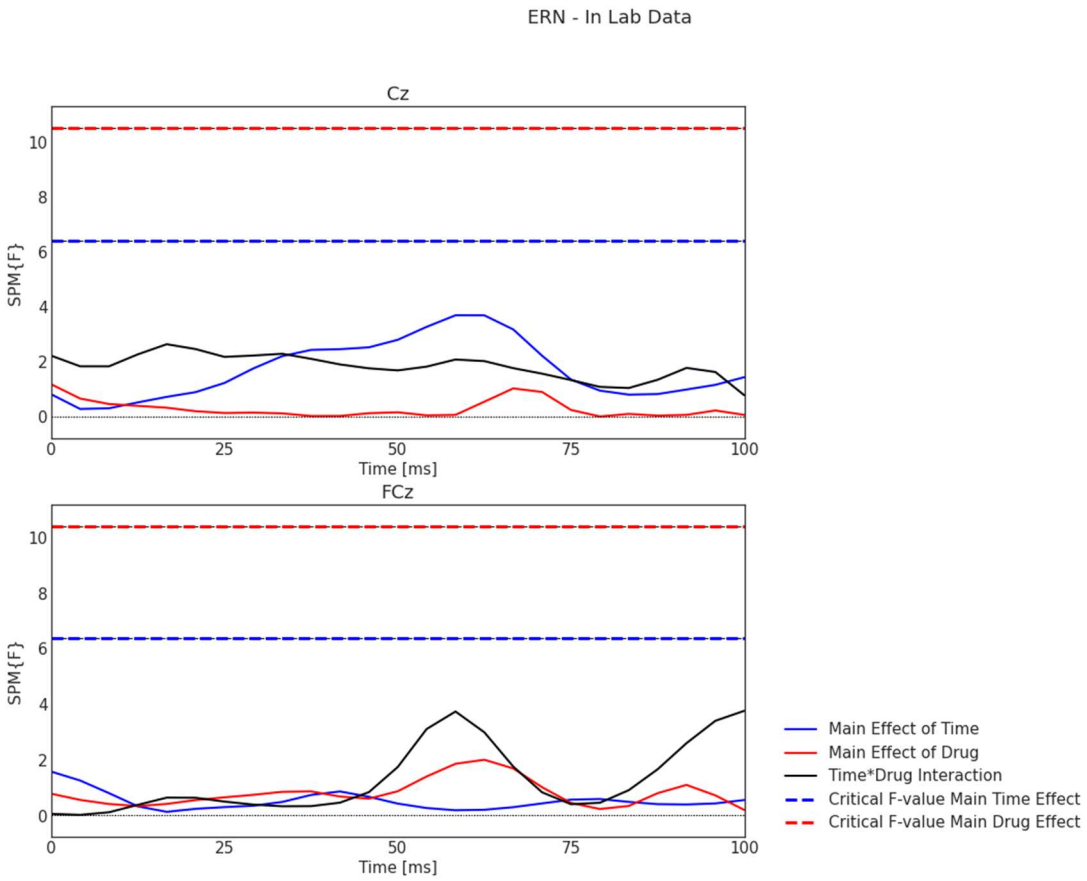


Figure 59: F-values extracted from the repeated Two-way ANOVAs on Go With The Flow data collected in the laboratory. Top row: Cz electrodes, bottom row: Pz electrode. Analyses of the ERN were conducted from 0 to 100ms time-window after participant's response. Shaded areas represent where the F-values reached the critical F-values. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes Cz and FCz included 24 and 26 participants, respectively.

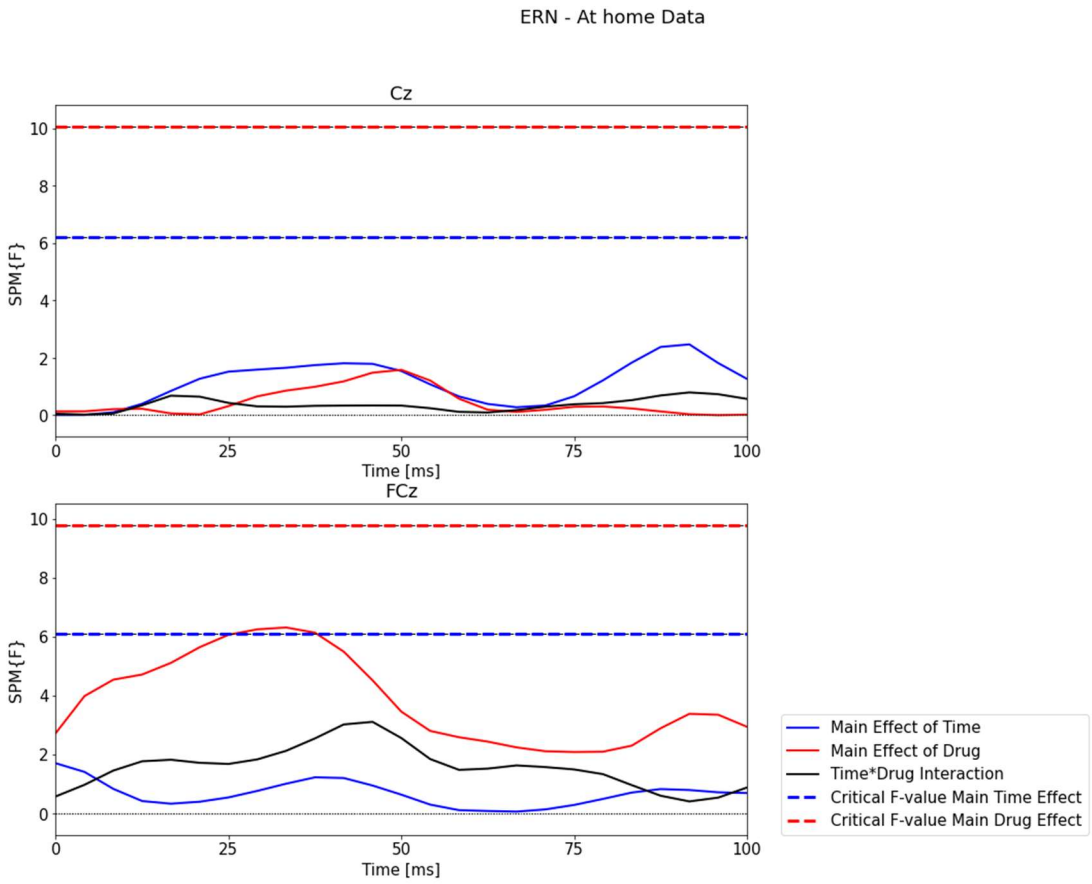


Figure 60: F-values extracted from the repeated Two-way ANOVAs on Go With The Flow data collected in the home. Top row: Cz electrodes, bottom row: Pz electrode. Analyses of the ERN were conducted from 0 to 100ms time-window after participant's response. The blue lines correspond to the F-values of the main effect of time, the red lines to the main effect of drugs, and the black lines to the Time*Drug interaction. Analyses at electrodes Cz and FCz included 25 and 29 participants, respectively.

4.4 Discussion

The first objective of this chapter was to replicate the well-studied acute effects of an infusion of racemic ketamine on cognition and brain function, as a proof-of concept of a novel data collection methodology. I also analysed the data collected over the days following the infusion to investigate any persistent drug effect. Data were extracted from a double-blind cross-over study on 30 young healthy male adults who received two infusions of either ketamine or saline solution four weeks apart. Brain and cognitive data were collected using a novel wireless dry EEG platform. It allowed participants to complete testing sessions in the laboratory under clinicians' supervision but also autonomously from the home at timepoints never explored after a ketamine intervention. Cognitive and brain data were collected via automated self-administered tasks delivered through android tablets. A total of 1,036 sessions were collected and EEG endpoints informative of attention, the excitatory:inhibitory balance, executive functions including decision making and error awareness, and early auditory memory were evaluated. Main acute and persistent ketamine effects on behaviour, resting brain activity and ERPs are discussed here.

The adherence and usability of the platform were previously discussed in the Empirical Chapter 1 of this thesis, as well as in the associated publication (Barbey *et al.*, 2022). Briefly, the usability and ease of use of the dry EEG platform was attested by the high adherence observed in the trial (over 99%; comprehensive adherence analyses are presented in section 3.3.2 of this thesis). Only one participant withdrew from the study because of reasons related to the technology (i.e., due to discomfort whilst wearing the headset). No more than 36 sessions were missed out of the 960 sessions requested per study protocol. We also note that a few participants submitted more sessions than requested. Total study data collection was completed under 3 months as the ease-of-use of the technology made it possible to complete up to 4 testing sessions per day in parallel in the clinic, with a single clinician supervising multiple participants. These results suggest that user-friendly wireless EEG technology has the potential to significantly accelerate pharmacological trials while dramatically reducing the total research cost. The technology can be acquired for a

fraction of the price of a traditional wet EEG system. Testing sessions can be parallelized, and participants can collect many more sessions from the home compared to standard ran in the laboratory pharmacological trials (Lau-Zhu, Lau and McLoughlin, 2019; McWilliams *et al.*, 2021).

The evaluation of resting state data collected during the infusion partially emulated the wet EEG literature. Specifically, I saw selective enhancement of the gamma band power during the second half of the infusion consistent with previous reports (Hong *et al.*, 2010; Muthukumaraswamy *et al.*, 2015; Shaw *et al.*, 2015; de la Salle *et al.*, 2016; Thiebes *et al.*, 2018; Nottage *et al.*, 2023). A trend toward a main significant effect of drug was also observed when evaluating the sessions collected in the laboratory 1 hr and 24 hrs after the infusions. Contrary to my initial hypothesis, no alpha power disruption were captured during the infusion despite it being a well-described and replicated result from the literature (Bojak, Day and Liley, 2013; de la Salle *et al.*, 2016; Vlisides *et al.*, 2018). This unexpected result may be related to the fact that the signals I aimed to capture had a small effect size. None of the ERP analyses revealed significant modulations by the drug immediately around the ketamine infusion which also refuted my initial hypotheses. I also did not observe any effects in the at-home dataset.

The broader discussion of the implications of the chapter are discussed in section 6.2.2 of the general discussion.

5 Empirical Chapter 3

Gamification of the visual Oddball task

5.1 Introduction

The gamification of standard laboratory cognitive paradigms is a booming field with many laboratories utilising this method as it increases sample size by improving participants' engagement and reducing attrition (Koo and Vizer, 2019; Hassenstab *et al.*, 2020; Germine *et al.*, 2021; Nicosia, Aschenbrenner, Adams, *et al.*, 2022). Smartphone-based studies report study protocol adherence between 57-85.7% depending on the duration of the study (Koo and Vizer, 2019), and acceptable-to-good retest reliability (Crump, McDonnell and Gureckis, 2013; Lipsmeier *et al.*, 2018; Berron *et al.*, 2022; Nicosia, Aschenbrenner, Adams, *et al.*, 2022). Several groups have demonstrated that gamified tasks can be used to detect age-related individual differences (McWilliams *et al.*, 2021; Berron *et al.*, 2022), can detect subtle cognitive impairments (Buckley *et al.*, 2017), discriminate healthy aging from genetically at-risk individuals of Alzheimer's disease (AD) (Coughlan *et al.*, 2019), and controls from Parkinson's disease patients (Lipsmeier *et al.*, 2018). Gamified tasks have successfully been deployed in large scale clinical research including the Australian Imaging, Biomarkers and Lifestyle (AIBL) study (Lim *et al.*, 2012) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Edgar *et al.*, 2021). Cross-sectional analyses revealed group differences between controls, participants suffering from mild cognitive impairment (MCI), and AD (Lim *et al.*, 2012; Valladares-Rodríguez *et al.*, 2016). Repeated testing enables longitudinal assessment and the capture of fluctuations in cognition (Wilks *et al.*, 2021). However, the validity of gamified cognitive tasks in combination with EEG, including their ability to elicit canonical ERP, has yet to be demonstrated.

One of the best studied ERPs in the EEG literature is the P300. It consists of a positive deflection occurring from approximately 300 ms after the presentation of a task-relevant stimulus (Dinteren *et al.*, 2014; Yerlikaya *et al.*, 2022). The term "P300" is used as an umbrella term to describe several related ERPs. The "P3a" has a centroparietal maximal amplitude, a short latency of 220 to 280 ms and is elicited by rare and frequent stimuli. The "P3b" component is more parietal and thought to be a task-relevant potential elicited during rare stimulus processing (Linden, 2005; Polich, 2007;

Barry, Steiner and De Blasio, 2016). The P3a amplitude decreases with repeated stimulus presentation and is thought to reflect connectivity between the frontal-lobe and hippocampus (Polich, 2007). The precise functional significance and neural underpinnings of the P300 remains unknown, although several frameworks have been proposed. The *context-updating theory* suggests that after sensory processing, the stimulus is compared to the previous element in working memory and a P300 is elicited if stimulus attributes changes are detected (Polich, 2007; San Martín, 2012). It is thought that the P300 amplitude is proportional to the amount of cognitive resource needed to update the model (San Martín, 2012). Familiarity related to previous exposure may modulate P300 components as some studies have observed smaller signals in response to novel stimuli (Polich, 2007). Other theories link the P300 to decision making processes relating to the stimulus evaluation and its subsequent mapping to appropriate responses (Nieuwenhuis, Aston-Jones and Cohen, 2005; Verleger, Jaśkowski and Wascher, 2005; Twomey *et al.*, 2015). Manipulating stimulus probability modulates the P300 amplitude, with larger amplitude associated with reduced probabilities of task-relevant stimuli (Polich, 2007). Furthermore, P300 amplitudes seem to be modulated by attentional resources, as reduction in amplitudes have been observed with reduced attentional resources (Kramer, Wickens and Donchin, 1985; Polich, 2007).

The P300 can be evoked by a wide variety of cognitive tasks including visual or auditory Oddball and Go/Nogo paradigms. Depending on the task and context of elicitation, it is thought that the P300 can reflect different or combined cognitive functions (Polich, 2007). Classical visual Oddball paradigms consist of presenting a rare "Target" stimulus requiring a response from the participant in the middle of a train of frequent stimuli to which participants are asked to not respond (i.e., "Non-Target" stimulus). On the other hand in Go/Nogo paradigms, participants are asked to respond to a frequently presented "Go" stimulus while withholding a response to a rare "Nogo" stimulus (Benikos, Johnstone and Roodenrys, 2013; Huster *et al.*, 2013). In both cases, participants are instructed to respond to one sort of visual stimulus which withholding a response to a second type of stimulus. The only difference between the two tasks are the frequencies of stimuli

presentation. The P300 produced by Nogo trials in Go/Nogo paradigm is referred to as the Nogo-P300 in the literature (Salisbury *et al.*, 2004; Polich, 2007; Enriquez-Geppert *et al.*, 2010). The Nogo-P300 is typically larger than the Go-P300 (e.g., elicited by Go trials) and is larger at frontal sites (Benikos, Johnstone and Roodenrys, 2013). It has been linked to motor inhibition, as well as other inhibitory subprocesses and is considered to reflect response inhibition (Albert *et al.*, 2013; Benikos, Johnstone and Roodenrys, 2013; Pires *et al.*, 2014).

The aim of this chapter was to evaluate the suitability of a gamified version of a standard laboratory task to elicit the P300. *Astrotap* is a gamified task based on the visual Oddball paradigm and has been designed to elicit the P300. Here, I qualitatively assessed subject-level ERPs captured across 10 participants to find out if *Astrotap* could elicit signals emulating the canonical P300 components as described in the literature, with higher topological resolution than was possible in the previously described studies (that used a low-density EEG montage). I evaluated ERP key features including morphology, peak amplitude, peak latency, and scalp topography. I examined clusters of electrodes located around the central line of the scalp, namely around Fz, FCz, Cz, CPz, and Pz. I hypothesised that Target trials would yield a P3b-like P300 signal while Non-Target trials would elicit a smaller positive deflection as intended by the task design. The rationale for the latter hypothesis was based on a classical 2-stimulus Oddball with rare Target trials and frequent Non Target trials (e.g. as described (Polich, 2007)). Thus, I expected to observe maximal amplitude around parietal regions for Target and Non-Target P300.

5.2 Methods

5.2.1 Participants

We recruited ten participants from the local community via word of mouth around Trinity College Dublin. Exclusion criteria were self-reported current or past diagnosis of neurological conditions (e.g. MS; epilepsy; depression; Parkinson's; dementia; or brain trauma), use of medication

including sedatives, anti-psychotics, anxiety medication, muscle relaxants, sleeping aids or medicines to treat seizures, current or past history of psychiatric treatment, current or past history of substance abuse, colour-blindness, and barriers to the technology integration into their home such as no WIFI connection or poor access to data network. All participants were compensated with a €50 voucher at the end of the study. The study was approved by the ethics committee of the School of Psychology of Trinity College Dublin, Ireland, and informed consent was obtained from all participants. Participants' data were collected, processed, and shared between sites according to the European General Data Protection Regulation (GDPR) and any applicable national privacy regulation.

5.2.2 Gamified visual Oddball task

The gamified visual Oddball paradigm Astrotap previously described in this thesis (see section 2.2.3.2) was used in this study.

5.2.3 Experimental Procedure

5.2.3.1 Study protocol

Participants were asked to complete a total of 19 sessions either in the laboratory or autonomously in the home. They were invited to the laboratory on two different occasions to complete repeated measurements while their brain activity was recorded using a wet EEG system: at enrolment (visit 1), and once again after completing the at-home phase of the study (visit 2).

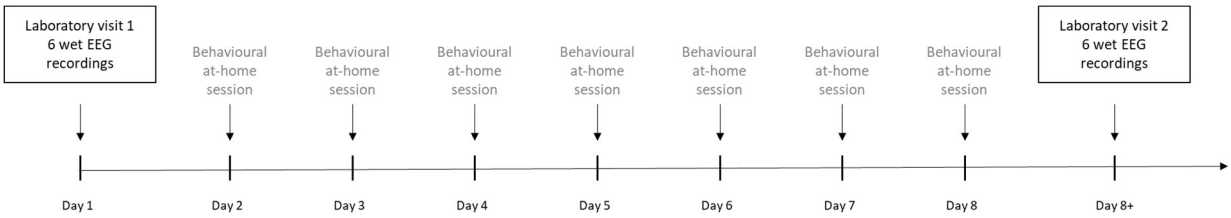


Figure 61: Diagram of the study design.

5.2.4 Laboratory visits

Upon arrival, all subjects signed an informed consent form after having the purpose and risks of the study explained and were set-up on a wet EEG system. During each laboratory visit, participants completed six consecutive gameplays; each lasting about 10 mins with a short break between gameplays. The total duration of these testing sessions was approximately 2 hrs and included consent (~10 mins), wet EEG set-up (~30 mins), testing (~60 mins), and clean-up (~20 min).

5.2.5 At-home data collection

Participants were instructed to perform seven recordings in the home after their initial study visit in the laboratory. Instructions indicated to complete one session per day, in a quiet place at a time where they would not be disturbed. The at-home task list included only one session of the gamified visual Oddball and lasted about 10 mins. No EEG was collected during these sessions, only behavioural data was recorded.

5.2.5.1 EEG acquisition

EEG data were recorded with a Biosemi ActiveTwo recording system (Biosemi B.V., Amsterdam, the Netherlands) with a 128-channel electrode cap conforming to the standard international 10–20 system of electrode placement. Each subject was tested individually inside a sound-attenuating and dim lighted chamber. Six external electrodes were used: four electrodes were placed around the eyes (on the side and under the eyes) to collect electro-oculogram (EOG) in the horizontal and vertical directions, and two on the mastoids. EEG was recorded at 512 Hz. Good signal quality from electrodes was ensured by experimenters during the setup by manual adjustment of individual electrodes and visual monitoring of output. Participants were instructed to sit in a comfortable position with both legs placed on the floor and asked to minimize eye movements during the gameplay. Participants were also asked to wait for the between-level and between-session breaks to make any movements.

5.2.5.2 Mobile app interface

The gamified Oddball task was delivered to the participants using a Huawei android tablet. Behavioural data was captured using the Cumulus mobile app (version 3.14.11). At the beginning of each session, participants logged in to the app using personal credentials supplied by the research team and were prompted to complete a gameplay. For the sessions completed under EEG, the technology provider supplied a custom-made ARDUINO board to connect to the wet EEG device ensuring the transmission of the stimulus and response markers to the Biosemi recording system.

5.2.6 Questionnaire

A month after the end of the study, participants were sent a debrief questionnaire to fill up via email. Questions pertained to the game strategy used by the participant throughout the trial and the impact of gameplay features on their behaviour.

5.2.7 Behavioural Analyses

All behavioural analyses were conducted using custom Python code (version 3.8.0). Reaction times (RT) to Target trials were extracted from the gamified Oddball. For each gameplay and participant, RT as well as accuracy to Target trial and to Non-Target trials were computed. Each behavioural measure was plotted across time for each participant.

5.2.8 EEG preprocessing

All EEG analyses were performed with custom Python code (version 3.9.12) implementing functions from the MNE package (version 1.1.0; https://mne.tools/stable/index.html). Raw EEG data was manually examined to identify and remove bad channels. Then, a Notch filter at 50 Hz, with a notch width of 2 Hz, was applied to remove powerline noise. A wide bandpass filter of 1 to 249 Hz was applied to optimize the signal for ICA decomposition and artefact correction as recommended by Gabard-Durnam and colleagues (Gabard-Durnam *et al.*, 2018). The filtered data was then epoched from 1 s before the onset of stimulus presentation to 2 s post-stimulus.

Individualized thresholds were used to reject epochs containing large muscle artifacts and extreme voltage offset. After that, epochs were decomposed into components using fastica ICA and manual component rejection was performed to extract muscular and ocular artifacts. The components to be rejected were first identified using the MNE-Python function "find_bad_eog" (see the function documentation at: https://mne.tools/stable/generated/mne.preprocessing.ICA.html#mne.preprocessing.ICA.find_bads_eog). This function was designed to detect EOG related components by correlating the EEG signals with the EOG signals recorded. The thresholding approach is based on adaptive z-scoring for which the default threshold was set at 3 (as recommended by the MNE function documentation). Then, the selected components were reviewed by a research assistant to ensure that they did not contain any brain data. For each component, its topographic map, time series and power spectrum density were reviewed to ensure that no brain data were removed. When there was an uncertainty about a component, a second person reviewed the component until a consensus was reached. The remaining components were then remixed and projected back to electrode space, and the resultant weights were applied to the previously filtered data (e.g., with a bandpass filter of 1 to 249 Hz). Then, a second narrower band pass filter of 0.1 to 30 Hz was applied and any epoch with amplitudes greater than 100 µV was removed. Only sessions with a minimum of 10 Target trials were included in the analyses. Finally, each epoch was re-referenced to an average reference and baselined using the mean epoch signal comprised within the -200 to 0 ms time-window.

5.2.9 ERP Analyses

ERPs were time-locked to the onset of the stimulus presentation and averaged within each condition. As this chapter consists in an exploratory qualitative analysis of ERPs, I computed separately for each individual: ERP images across all the in-laboratory sessions, topographic maps, and ERPs trace for Target and Non-Target conditions. The qualitative evaluation of the ERPs covered five attributes: the ERP morphology, timing, topographical distribution, relative

amplitude of Target vs. Non-Target signals, and the emergence or not of consistent patterns with task repetition.

5.3 Results

5.3.1 Recruitment and participant inclusion

A total of 10 participants (mean age=25.3 years; 3 females) were recruited from the local community. However, four participants had to be excluded from the analyses due to very low EEG data quality. The reasons for the low data quality were: one participant arrived extremely tired on one of the testing days and their EEG was dominated by alpha waves which made it unusable, one participant exhibited a male pattern baldness and their EEG signals were abnormally small, two participants had to be excluded because of too many muscular and movement artefacts in the datasets. The final sample included six participants (mean age= 25.7 years; 3 females).

5.3.2 Subject 1

Subject 1 was a 25-year-old right-handed male. Their questionnaire revealed that their game strategy did not change during the course of the study. They reported prioritizing accuracy over speed. Their mean RT was 329.6ms (SD=15.3 ms), mean accuracy to target trials was 99.8% (SD=0.8%), and mean accuracy to Non-Target trial was 99.2% (SD=1.0%). Behavioural data from Subject 1 are presented on Figure 62.

5.3.2.1 Questionnaire

	Subject 1
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	No, I just focused on shooting aliens and stars all the time.
If so, would you be able to say when?	N/A
Did any of the game features (such as points or bonus stars) impact your game strategy?	No
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	Yes
Did you prioritize speed and accuracy equally?	No

Table 20: Questionnaire data from Subject 1.

5.3.2.2 Behavioural analysis

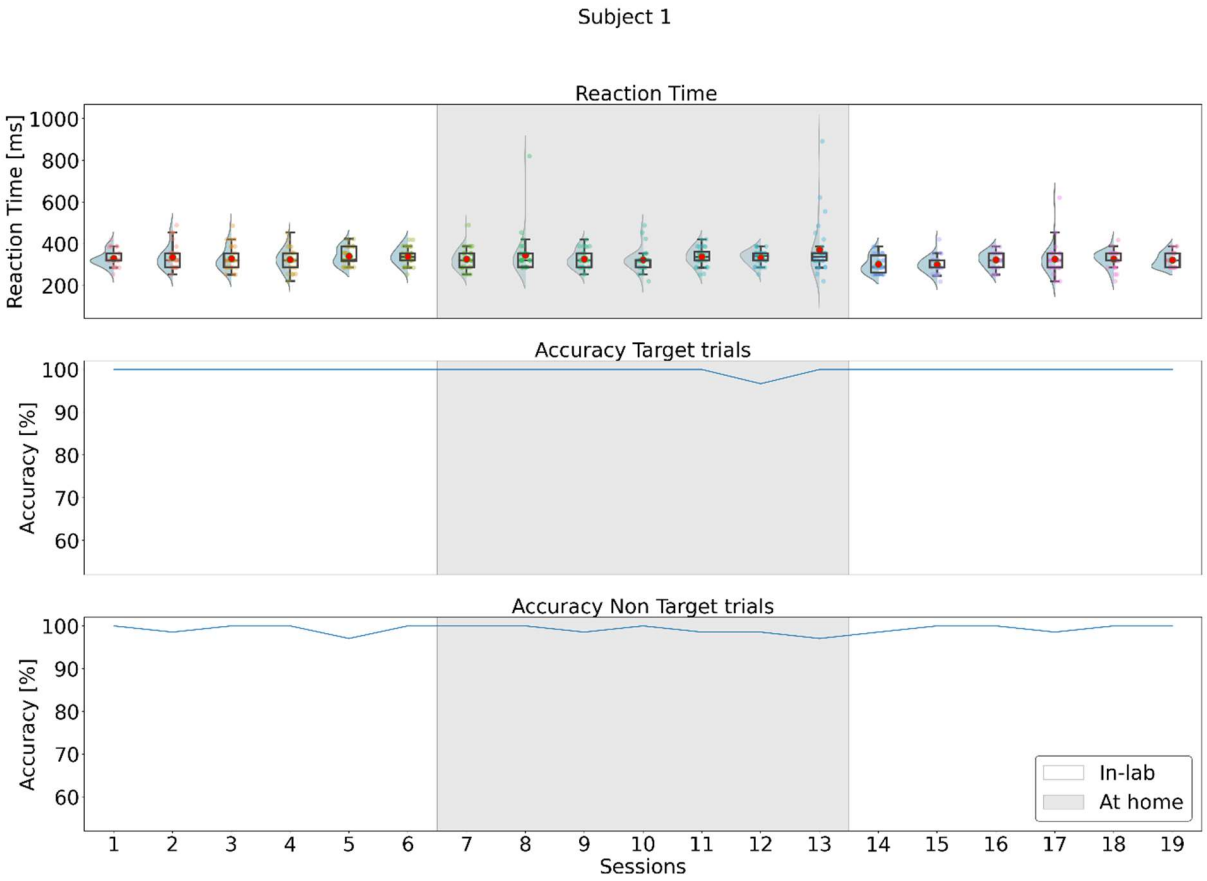


Figure 62: Behavioural responses of Subject 1. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.2.3 EEG analysis

EEG data of Subject 1 are presented in Figures 63 to 69. Both for Target and Non-Target trials, one can observe the typical positive deflection of the P300 occurring around 300 ms post stimulus presentation; just after early sensory perceptual components happening between 0 to 250 ms. The topography of the signals seems to be consistent across conditions with both Target and Non-Target trials peaking around central regions. The amplitudes of the P300 extracted from Target trials are larger than the ones extracted from Non-Target trials as demonstrated by the positive the difference waves presented in Figures 64 and 65. When examining the ERP image (Figure 63) and the topographic maps (Figures 66 to 69), it appears that the amplitudes of the Target and Non-Target signals could be decreasing across sessions and days.

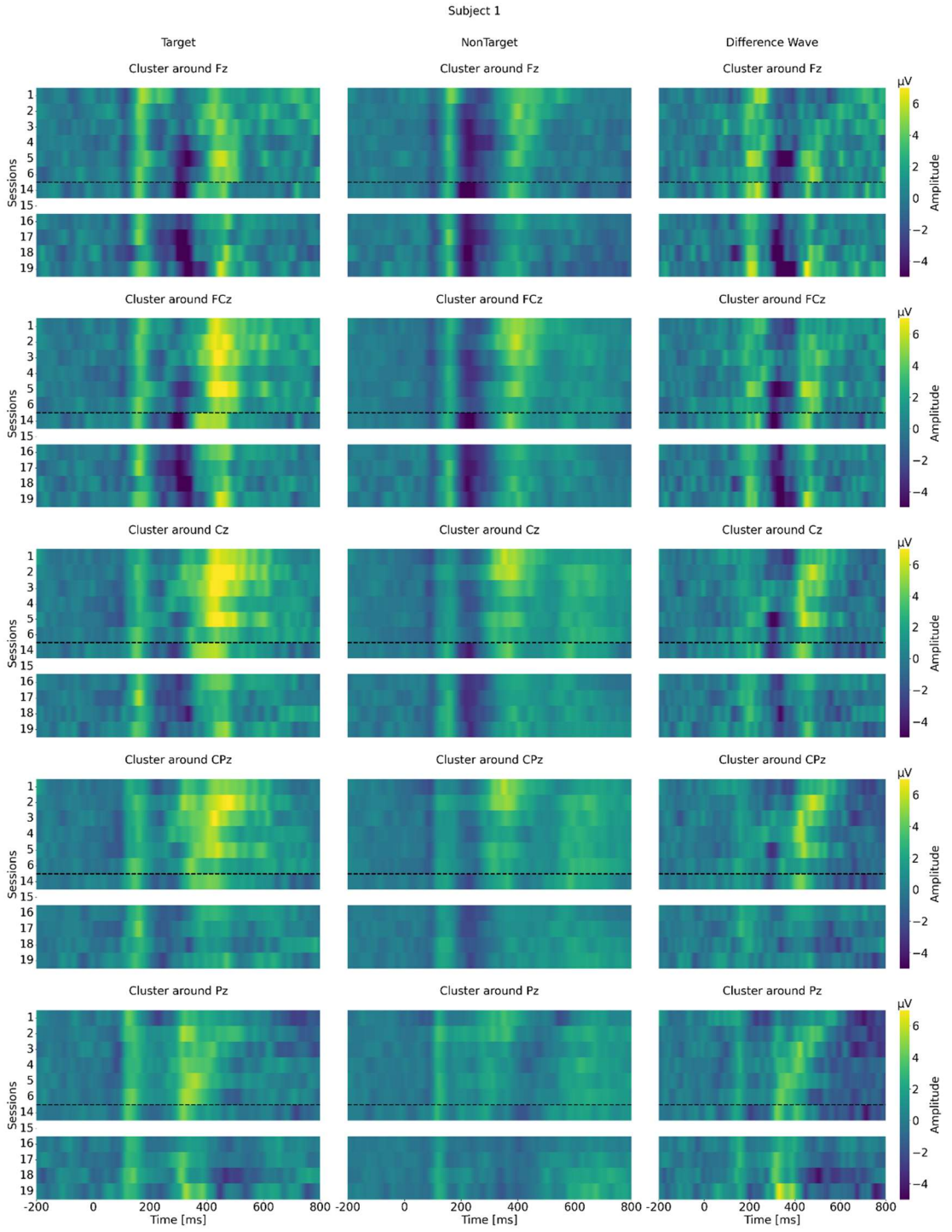


Figure 63: Mean event-related potentials for each session extracted around clusters of interest for Subject 1. Each line of a plot represents a session. Each row of the Figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

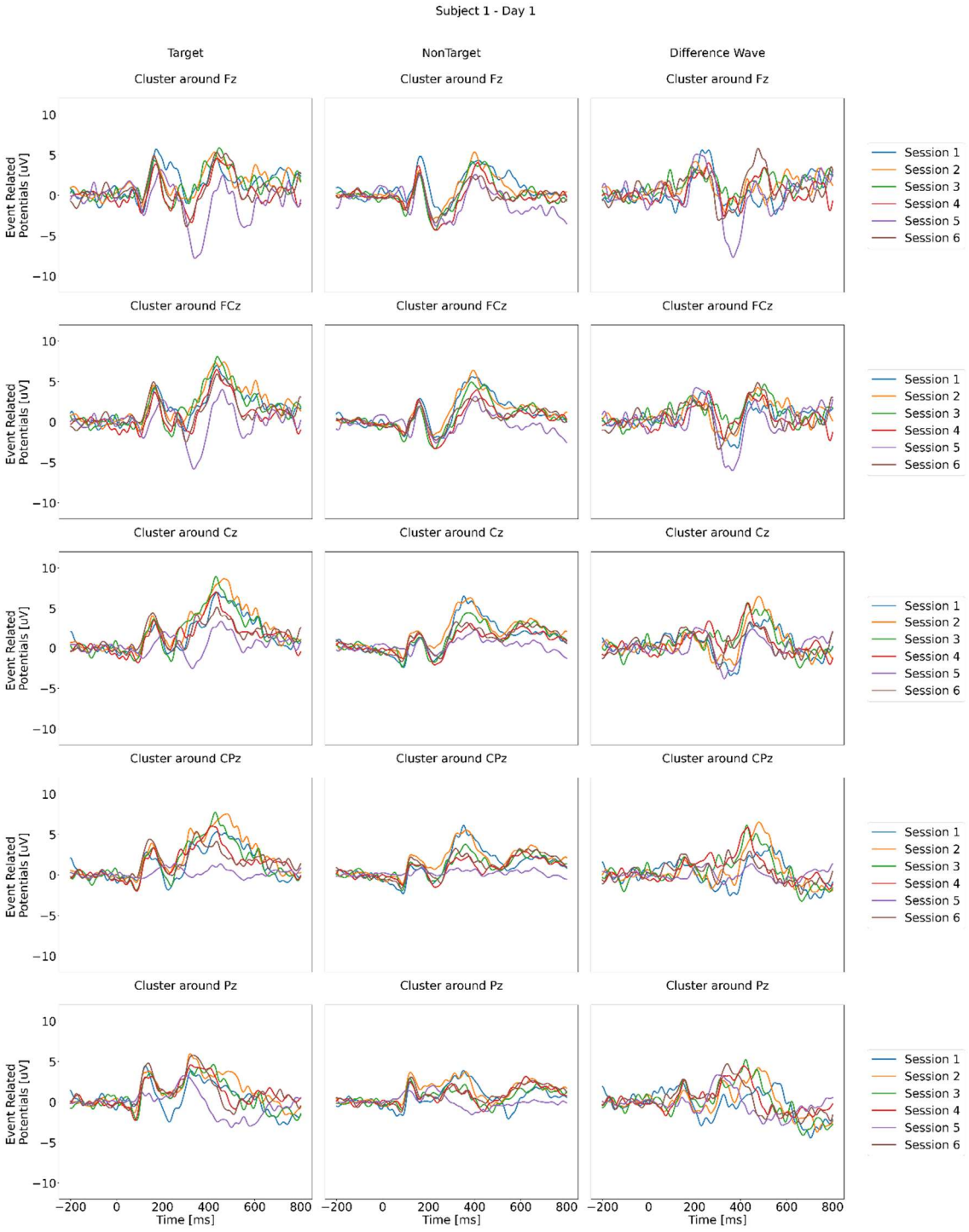


Figure 64: Event related potentials traces around clusters of electrodes of interest for Subject 1 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

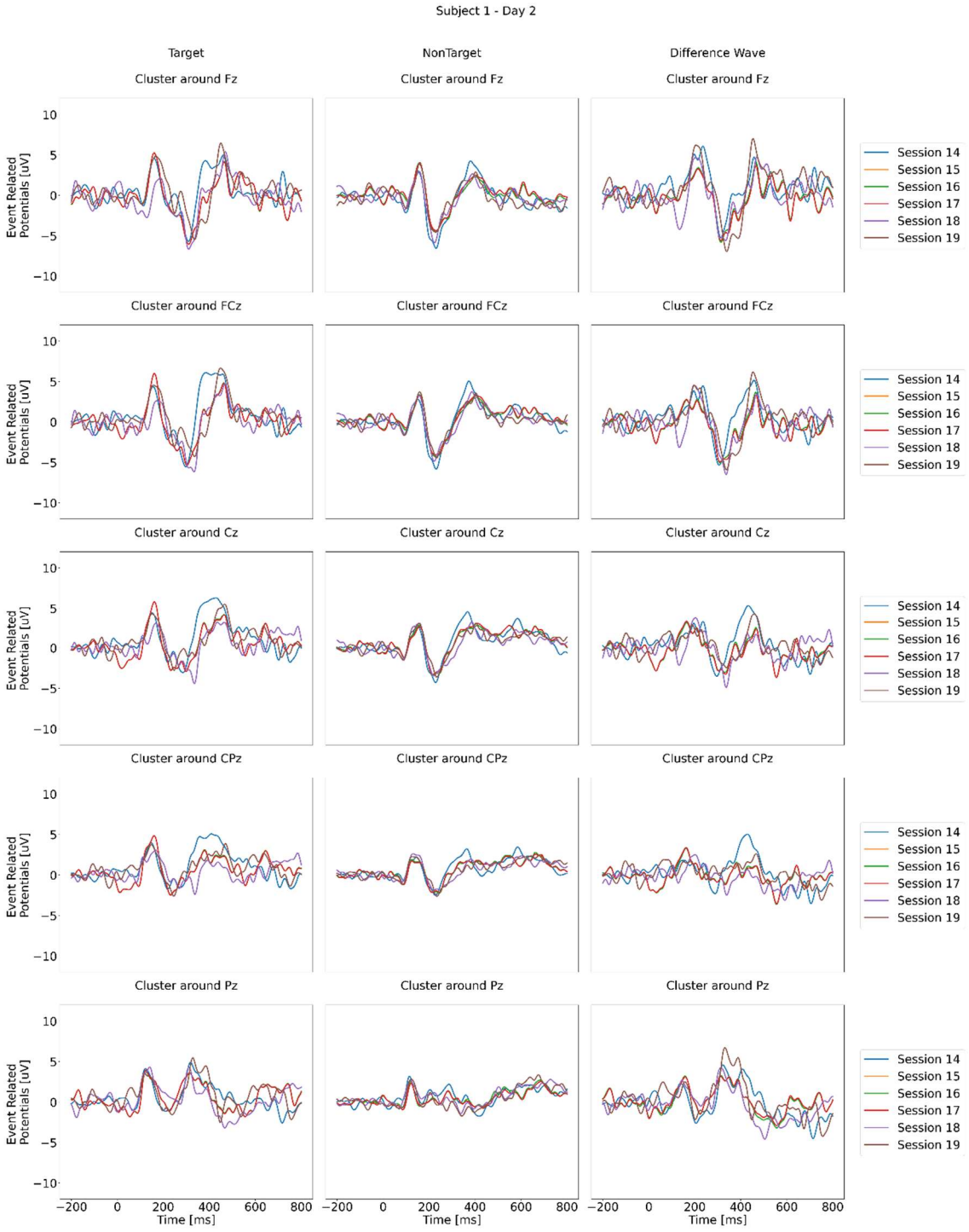


Figure 65: Event related potentials traces around clusters of electrodes of interest for Subject 1 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

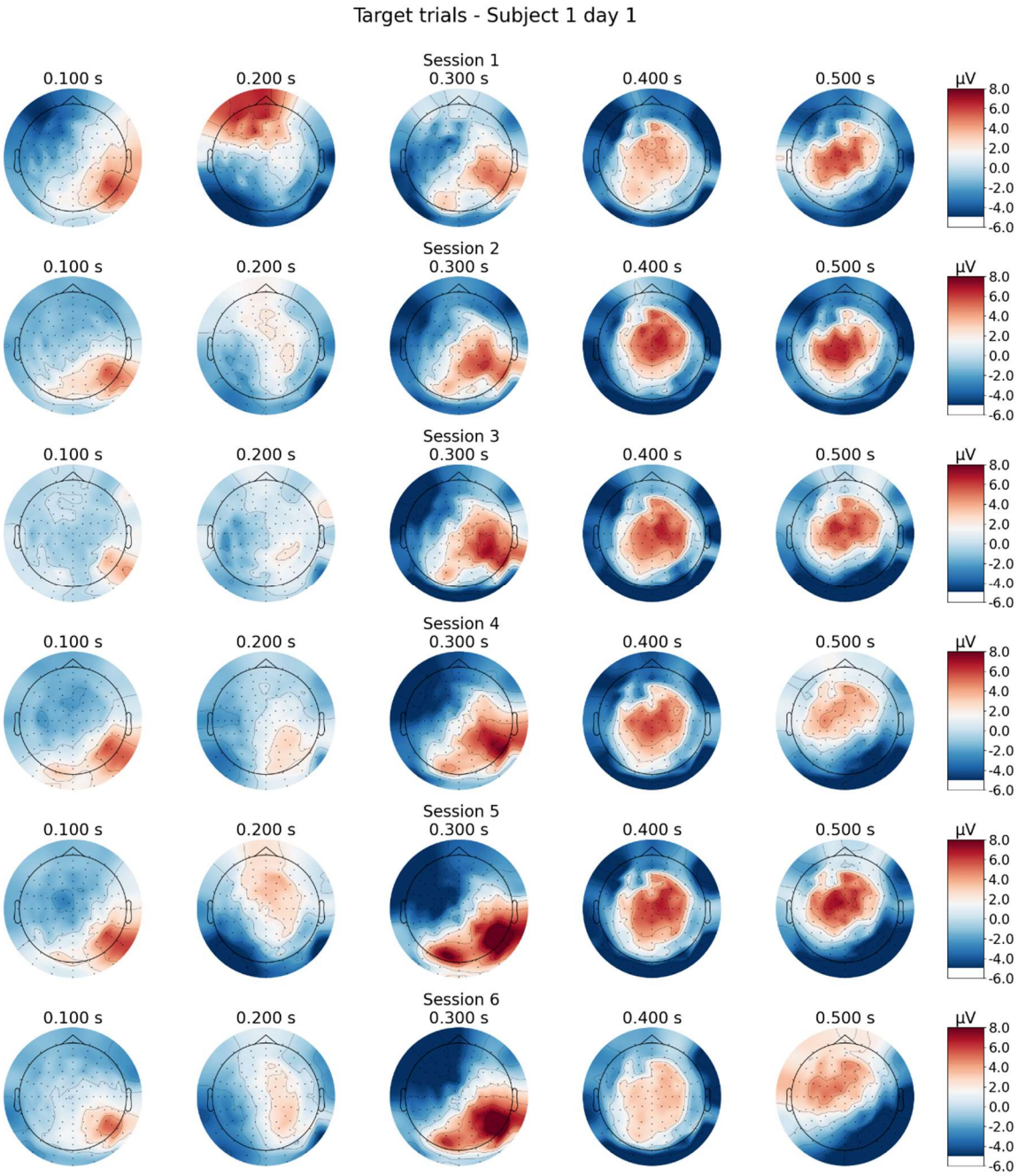


Figure 66: Topographic maps of event related potentials of Subject 1 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

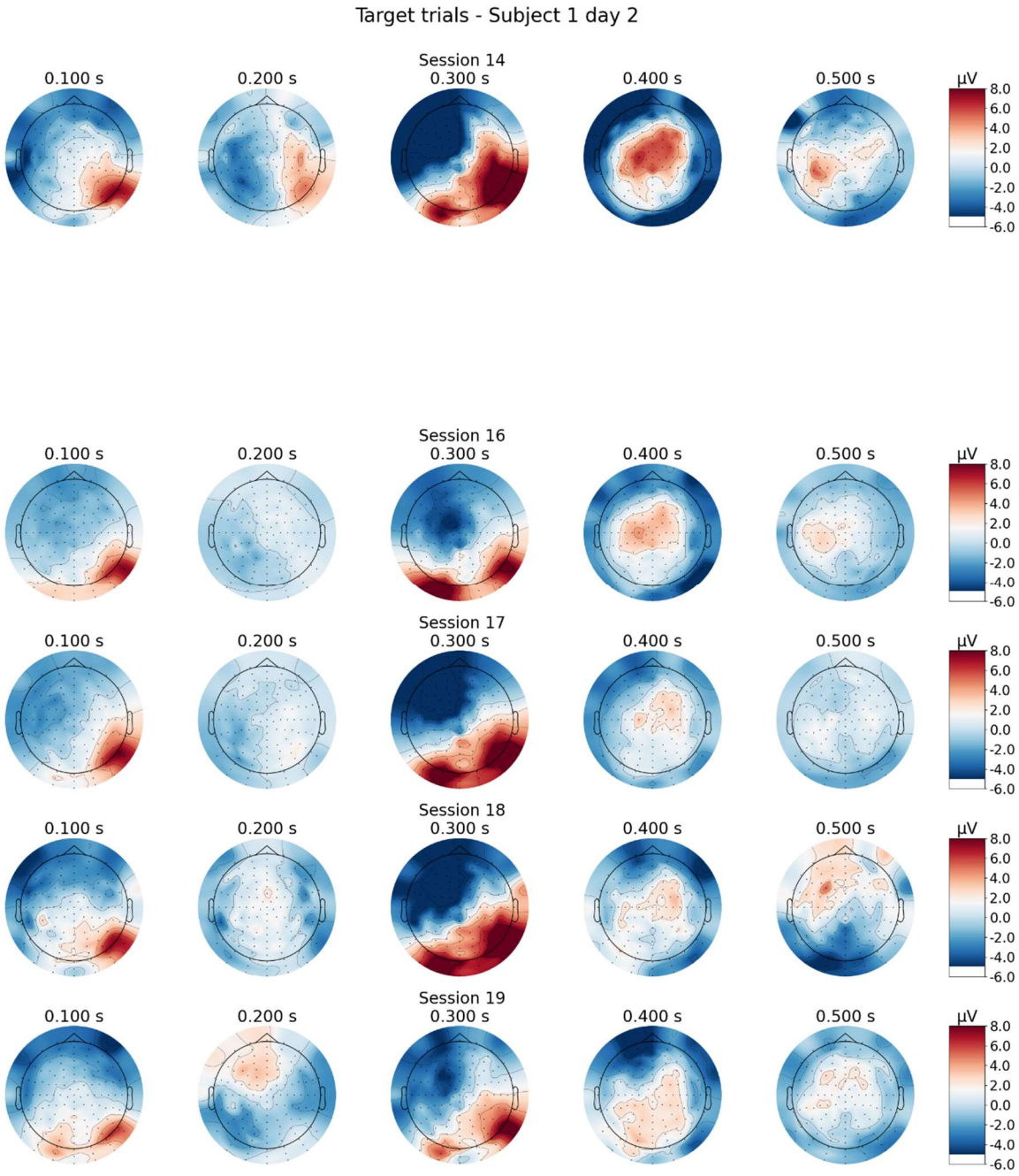


Figure 67: Topographic maps of event related potentials of Subject 1 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

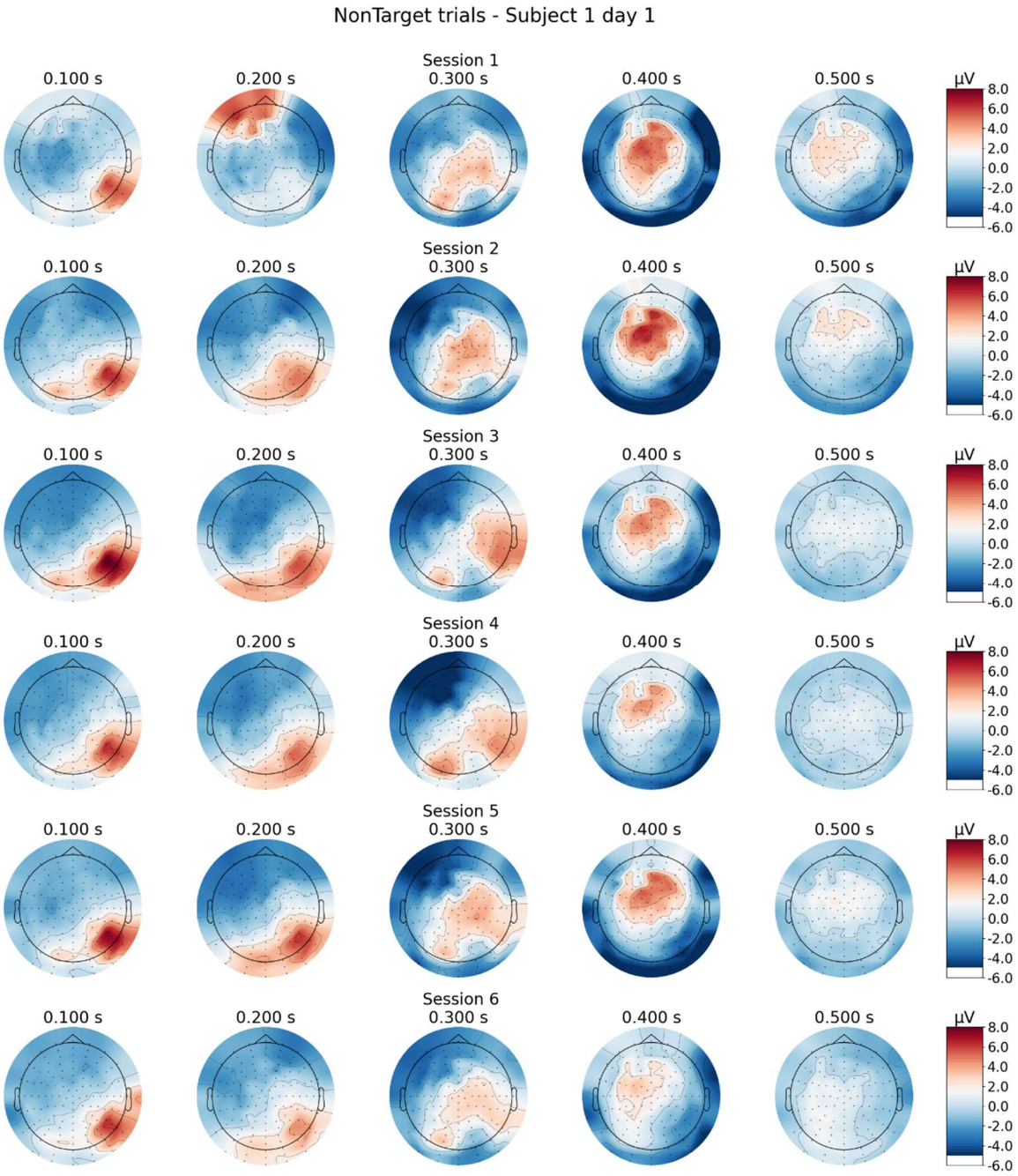


Figure 68: Topographic maps of event related potentials of Subject 1 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

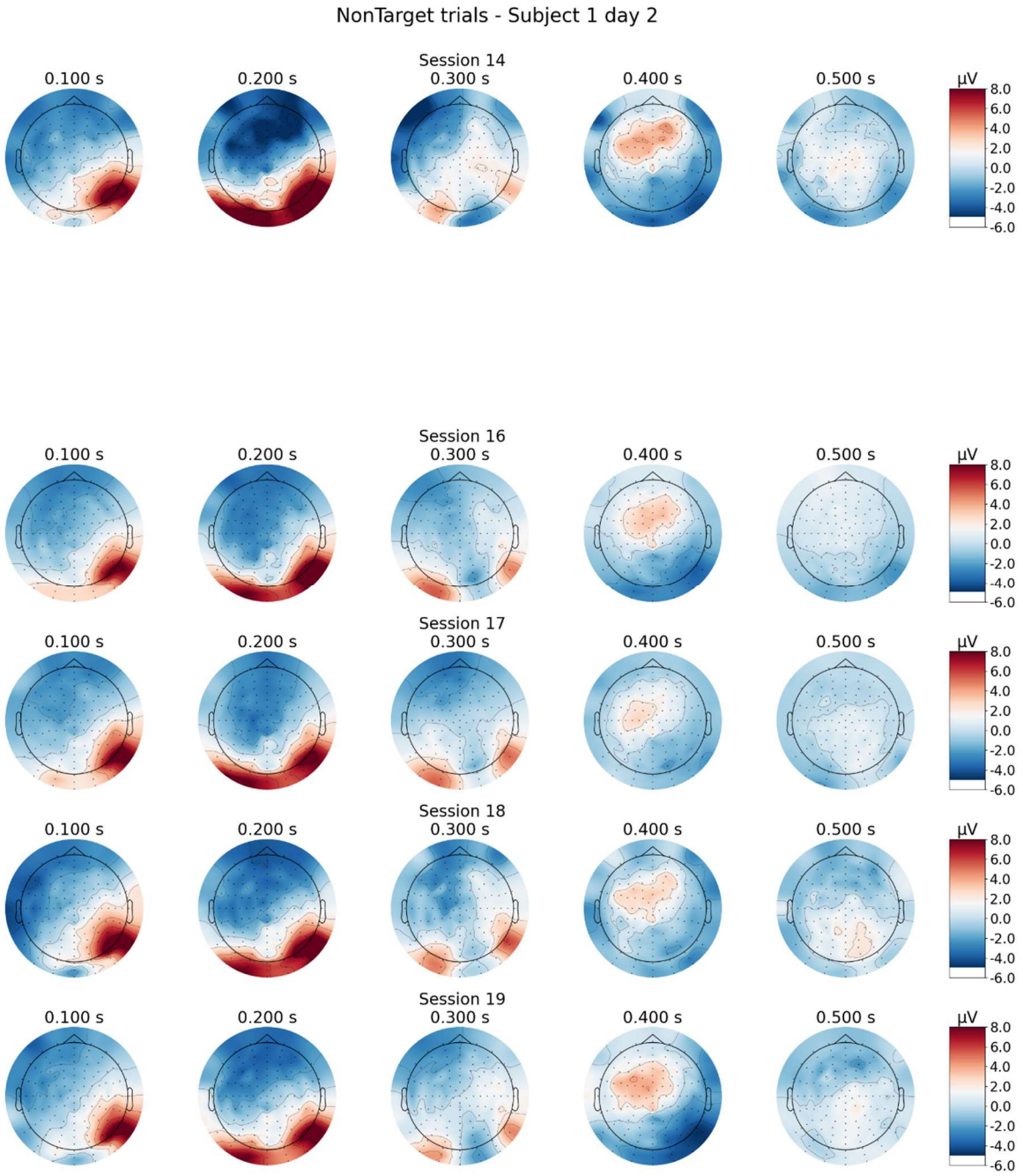


Figure 69: Topographic maps of event related potentials of Subject 1 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.3 Subject 2

Subject 2 was a 25-year-old right-handed female. Their questionnaire revealed that their strategy while playing the game throughout the study did not change. They reported prioritizing accuracy and speed equally. Their mean RT was 299.3ms (SD=20.0ms), mean accuracy to target trials was 100% (SD=0%), and mean accuracy to Non-Target trial was 97.9% (SD=1.5%). Behavioural data from Subject 2 are presented on Figure 70.

5.3.3.1 Questionnaire

	Subject 2
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	I did try and experiment and realized the strategy I started with worked the best for me anyway
If so, would you be able to say when?	Not exactly, but towards the earlier stages. I finished all sorts of experimenting by the mid-stages and stuck to the one that worked best for me.
Did any of the game features (such as points or bonus stars) impact your game strategy?	Oh yes, I was trying to shoot the aliens as fast as I could because that had more points, but the downside was I shot a few astronauts in the process if I got even a little distracted.
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	No
Did you prioritize speed and accuracy equally?	Yes

Table 21: Questionnaire data from Subject 2.

5.3.3.2 Behavioural analysis

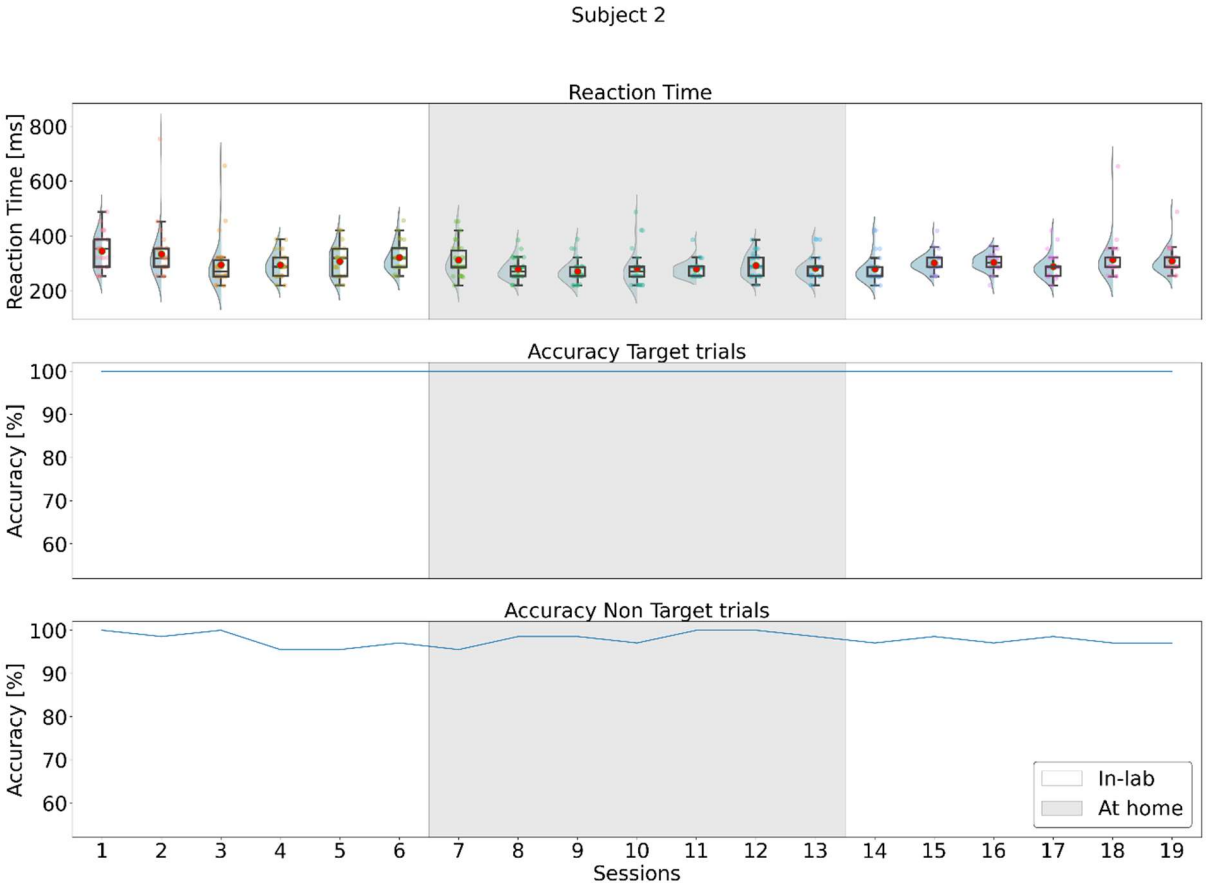


Figure 70: Behavioural responses of Subject 2. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.3.3 EEG analysis

EEG data of Subject 2 are presented on Figures 71 to 77. First, there were clear differences in signal amplitudes between the first and second testing days around the clusters of electrodes Cz and CPz in the ERP image (Figure 71) and in the ERP traces (Figures 72 and 73). On the day of testing, the experimenters reported observing unusually high levels of noise in the ribbon of electrodes corresponding to the Cz and CPz clusters. Because of this reason, qualitative analyses are restricted to the first in-laboratory visit.

The typical positive deflection of the P300 occurring after the early sensory perceptual components around 400ms is only observed in the Non-Target condition. The Target signals are akin to a slow positive drift rather than a true peak. The topography of the Non-Target P300 is consistent across sessions and peaks in frontocentral regions. The topography of the Target signal seems to be bilateral. The amplitudes of the Non-Target trials are larger than the ones extracted from Target trials as demonstrated by the negative the difference waves presented in Figures 72 and 73. When examining the ERP image (Figure 71) and the topographic maps (Figures 74 to 77), it seems that the amplitudes of the Non-Target signals is consistent across sessions.

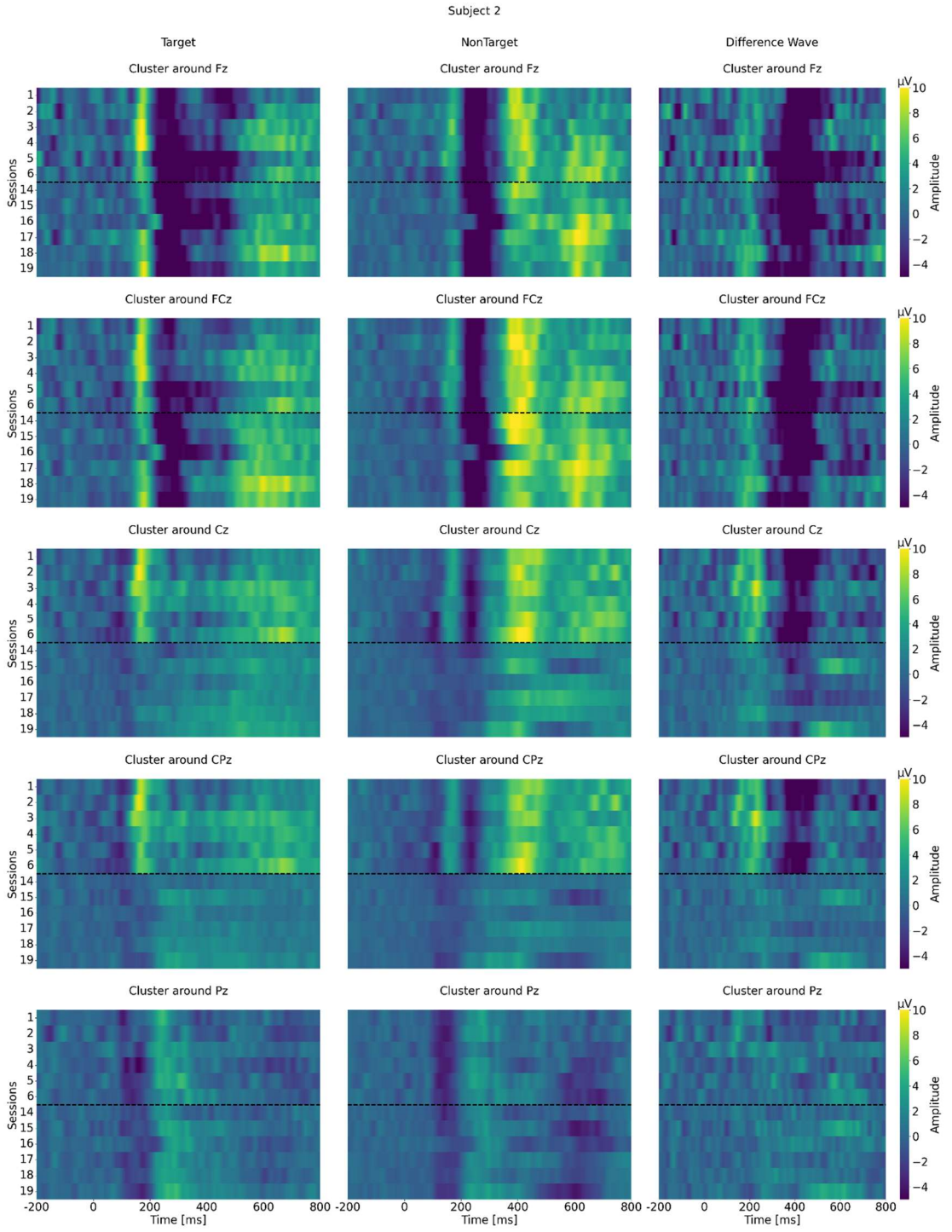


Figure 71: Mean event-related potentials for each session extracted around clusters of interest for Subject 2. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

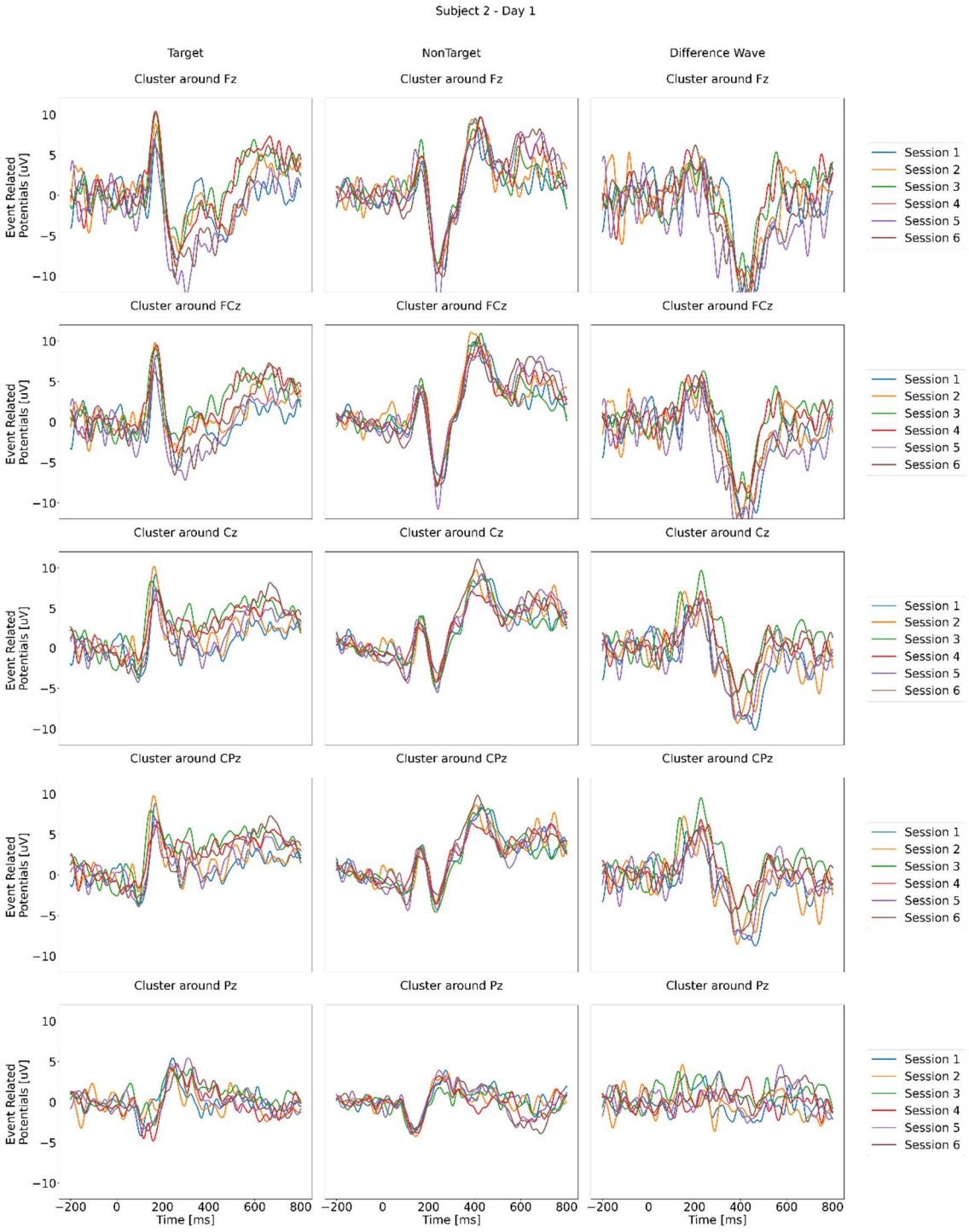


Figure 72: Event Related potentials traces around clusters of electrodes of interest for Subject 2 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

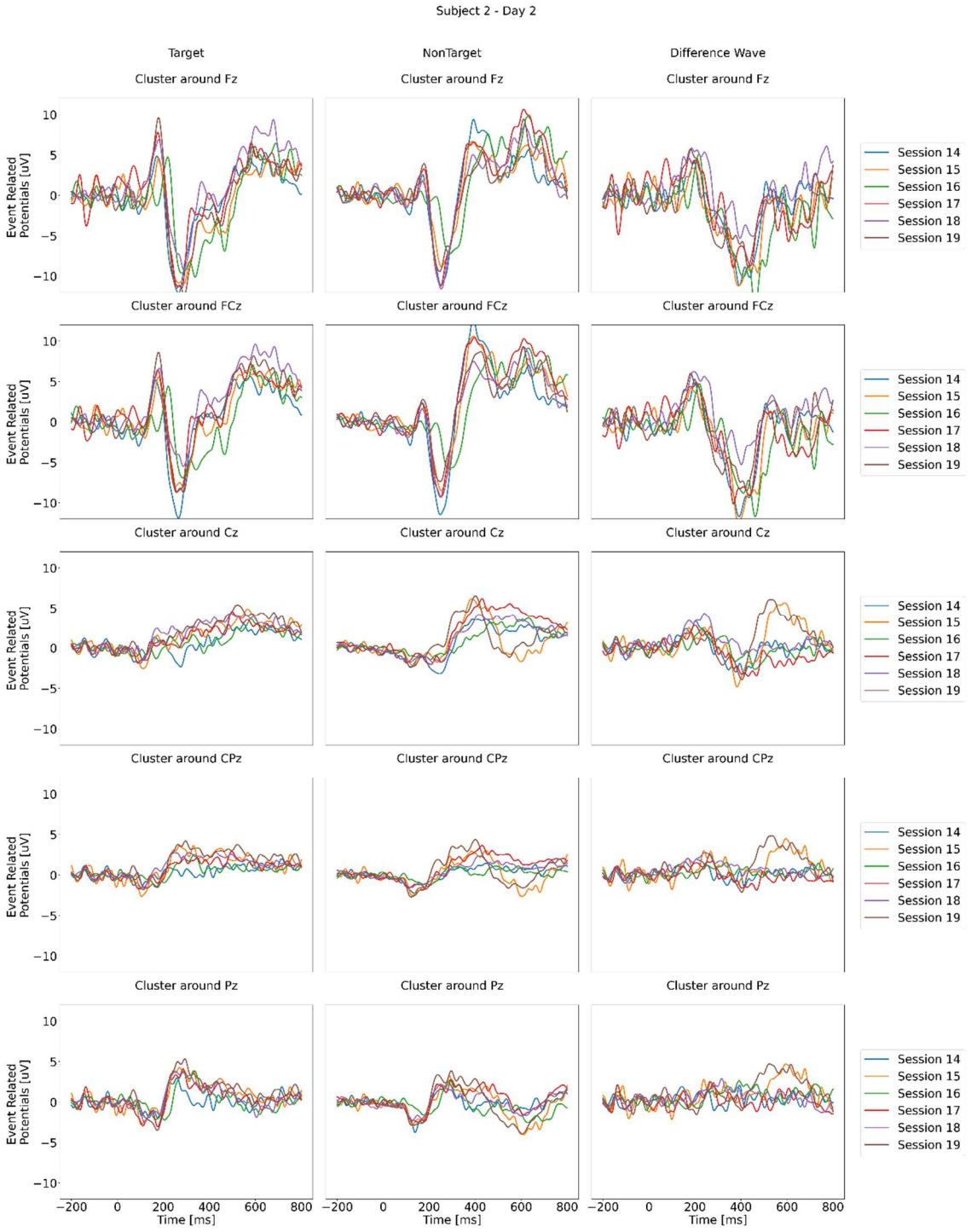


Figure 73: Event Related potentials traces around clusters of electrodes of interest for Subject 2 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

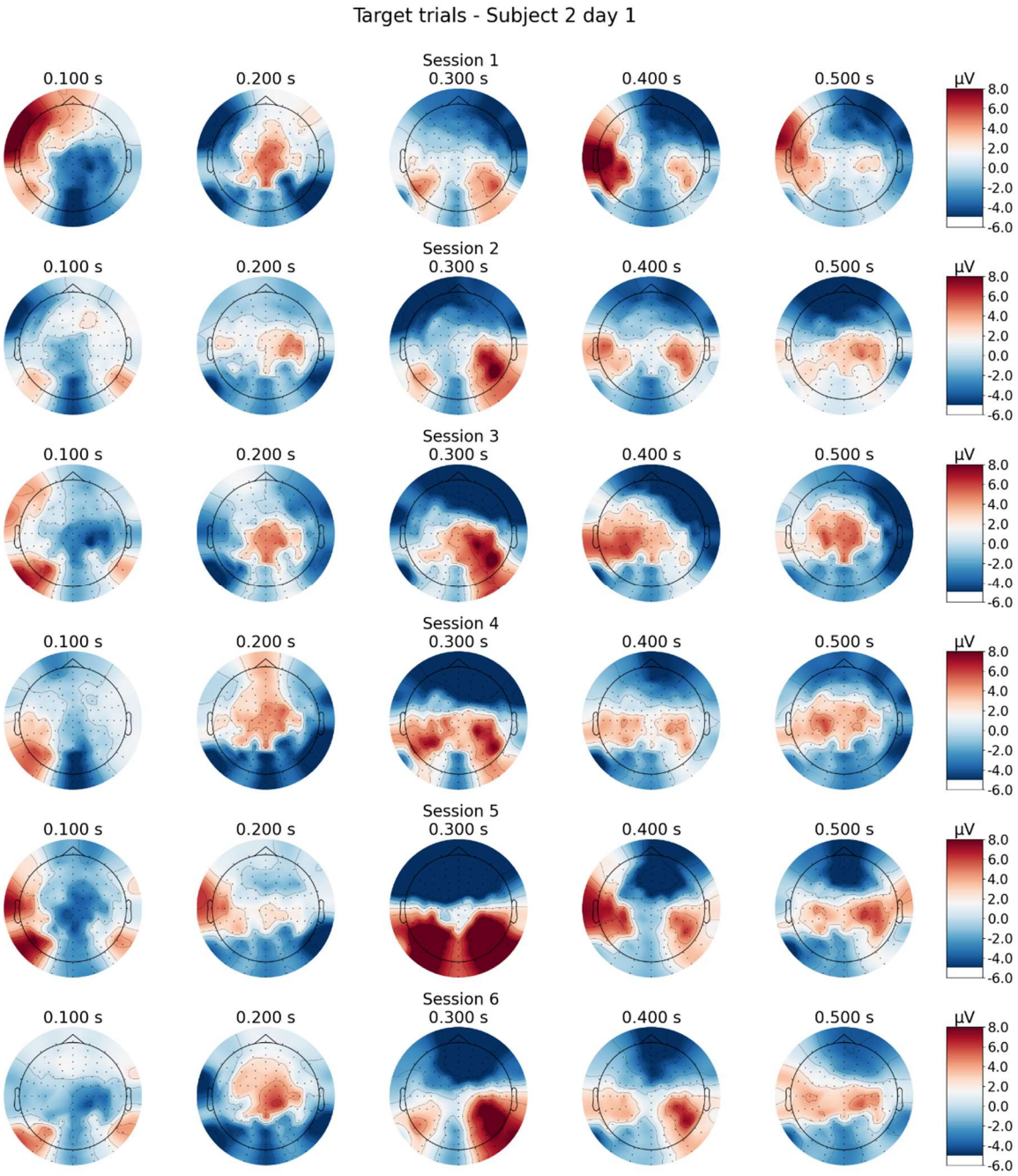


Figure 74: Topographic maps of event related potentials of Subject 2 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

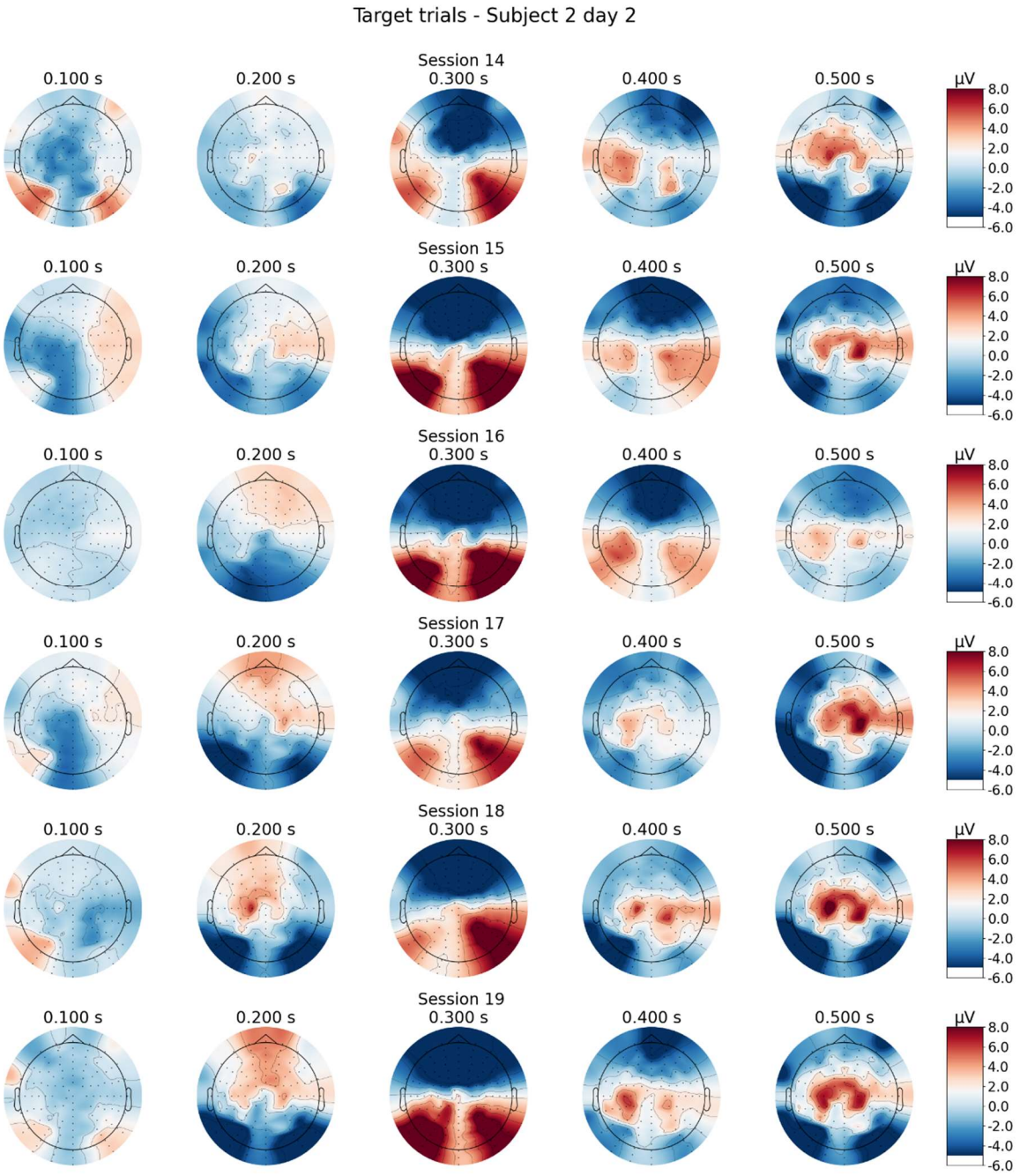


Figure 75: Topographic maps of event related potentials of Subject 2 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

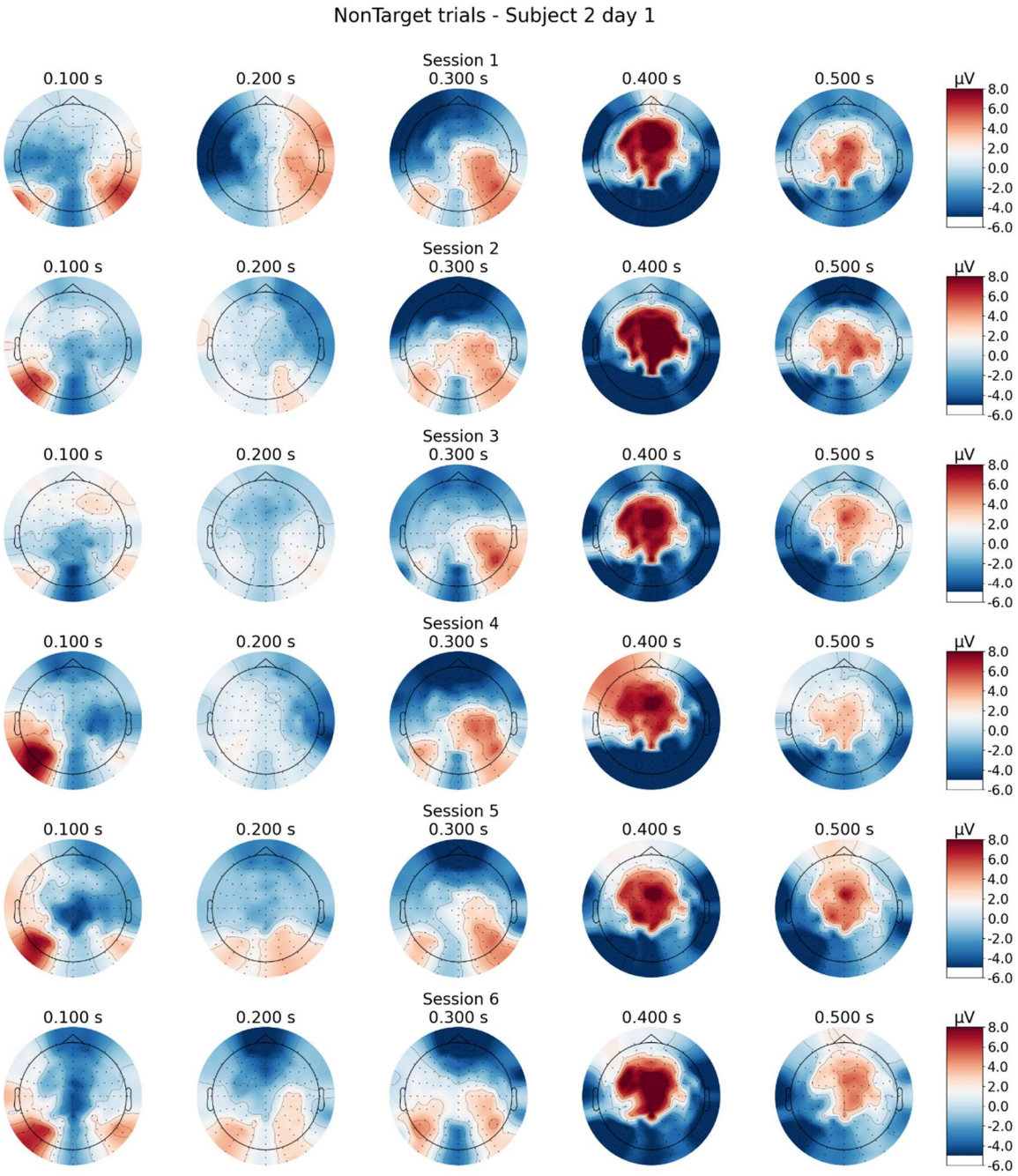


Figure 76: Topographic maps of event related potentials of Subject 2 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

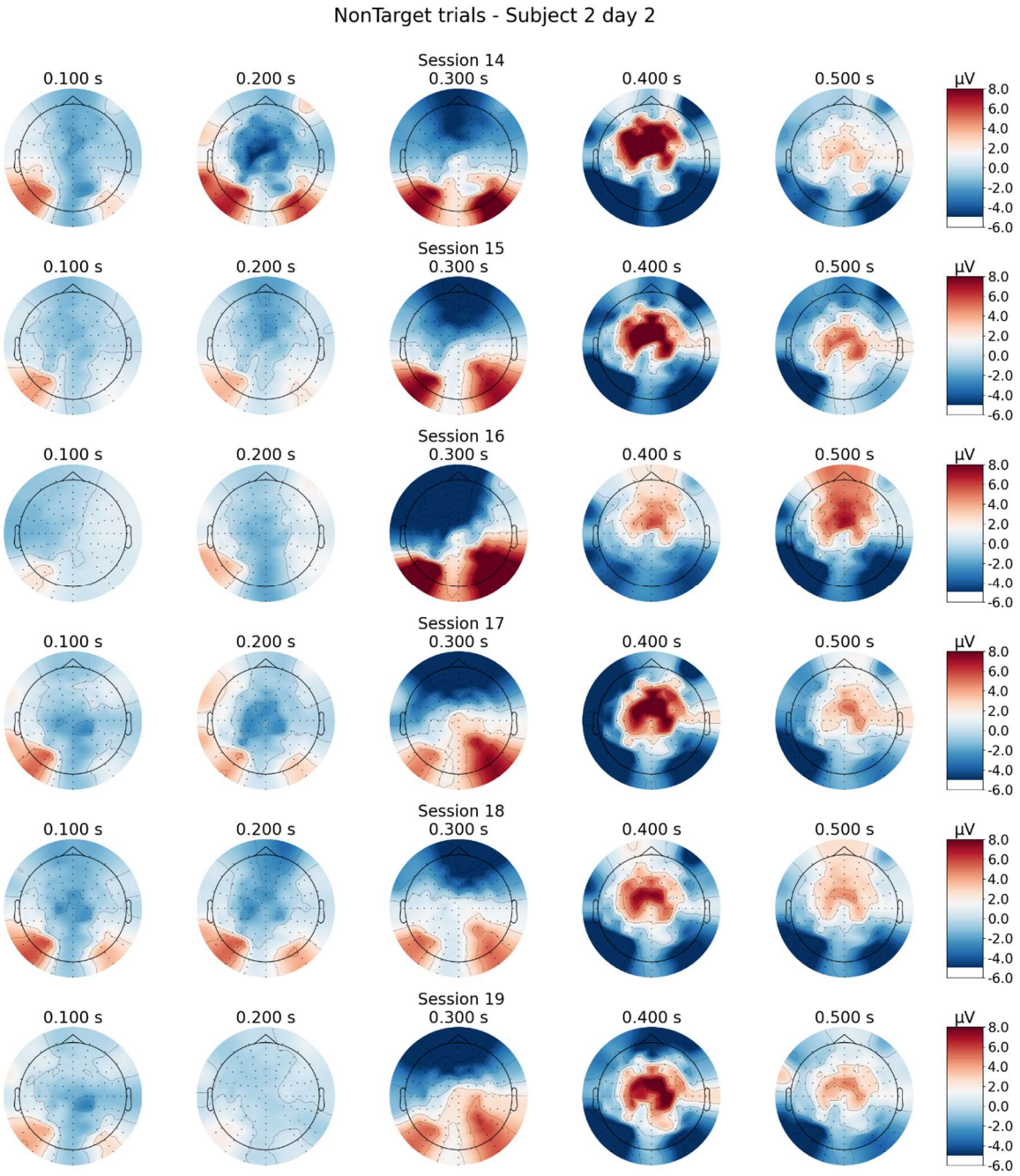


Figure 77: Topographic maps of event related potentials of Subject 2 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.4 Subject 3

Subject 3 was a 22-year-old right-handed female. Their questionnaire revealed that their game strategy changed during the course of the study. They reported first focusing on responding to Target stimulus and later on focused on avoiding responding the Non-Target stimulus after getting habituated to the game. They reported prioritizing speed over accuracy. Their mean RT was 382.9ms (SD=28.2ms), mean accuracy to target trials was 99.6% (SD=1.1%), and mean accuracy to Non-Target trial was 99.2% (SD=1.1%). Behavioural data from Subject 3 are presented on Figure 78.

5.3.4.1 Questionnaire

	Subject 3
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to avoid astronauts rather than shooting aliens
Can you remember if your strategy changed at some point during the study?	Yes
If so, would you be able to say when?	When I got a kind of habituation effect to the game and the rules
Did any of the game features (such as points or bonus stars) impact your game strategy?	Yes, the stars motivated me I refocused my attention.
Did you prioritize speed over accuracy?	Yes
Did you prioritize accuracy over speed?	No
Did you prioritize speed and accuracy equally?	No

Table 22: Questionnaire data from Subject 3.

5.3.4.2 Behavioural analysis

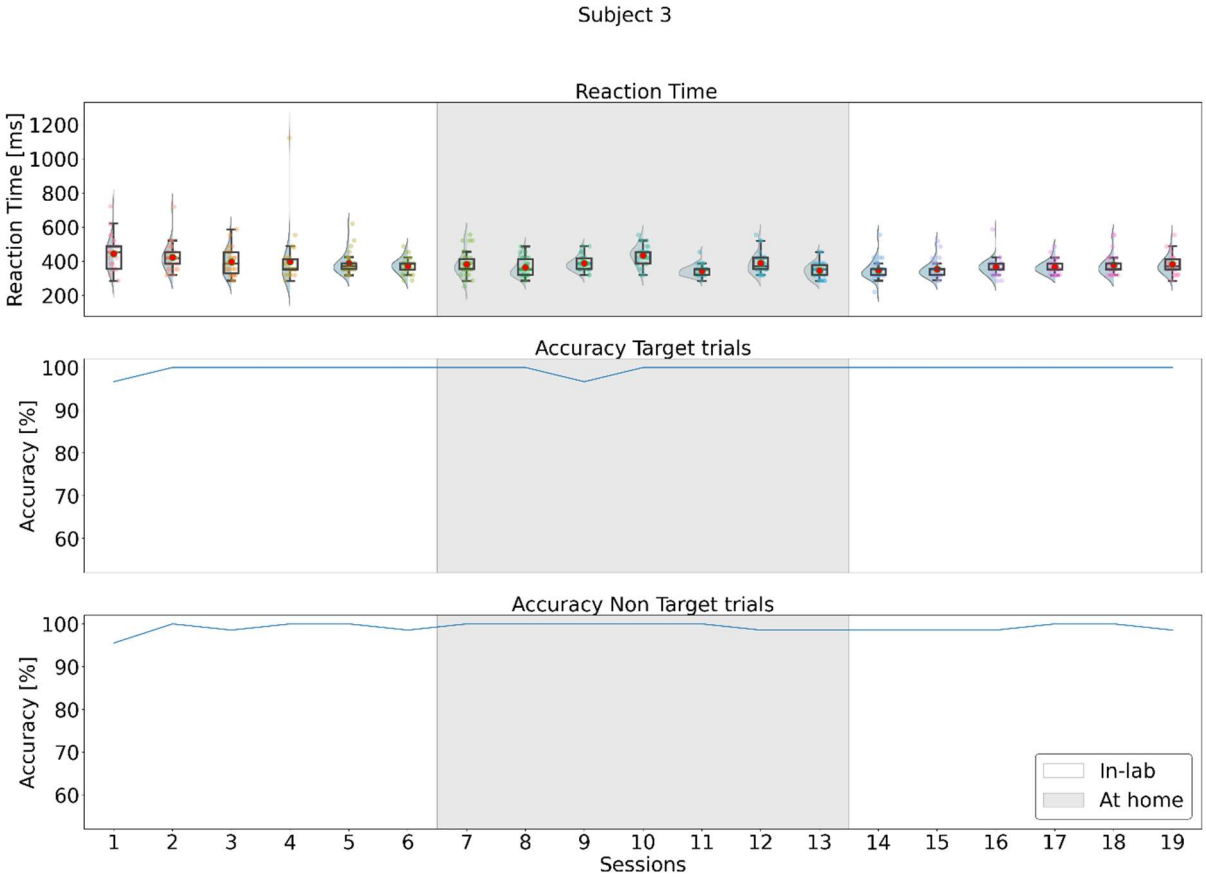


Figure 78: Behavioural responses of Subject 3. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.4.3 EEG analysis

EEG data of Subject 3 are presented on Figures 79 to 85. Both for Target and Non-Target trials, the typical positive deflection of the P300 occurring can be observed around 300 ms post stimulus presentation; just after early sensory perceptual components happening between 0 to 250 ms, although it should be noted that amplitudes are overall quite small. The topography of the signals seems to be consistent within conditions with Target signals peaking around centro-parietal regions and Non-Target trials peaking around central regions. The amplitudes of the Non-Target trials are larger than the ones extracted from Target trials as demonstrated by the negative the difference waves presented in Figures 80 and 81. When examining the ERP image (Figure 79) and the topographic maps (Figures 82 to 85), it is difficult to discern a clear pattern of amplitude modulation across time both for the Target and Non-Target condition.

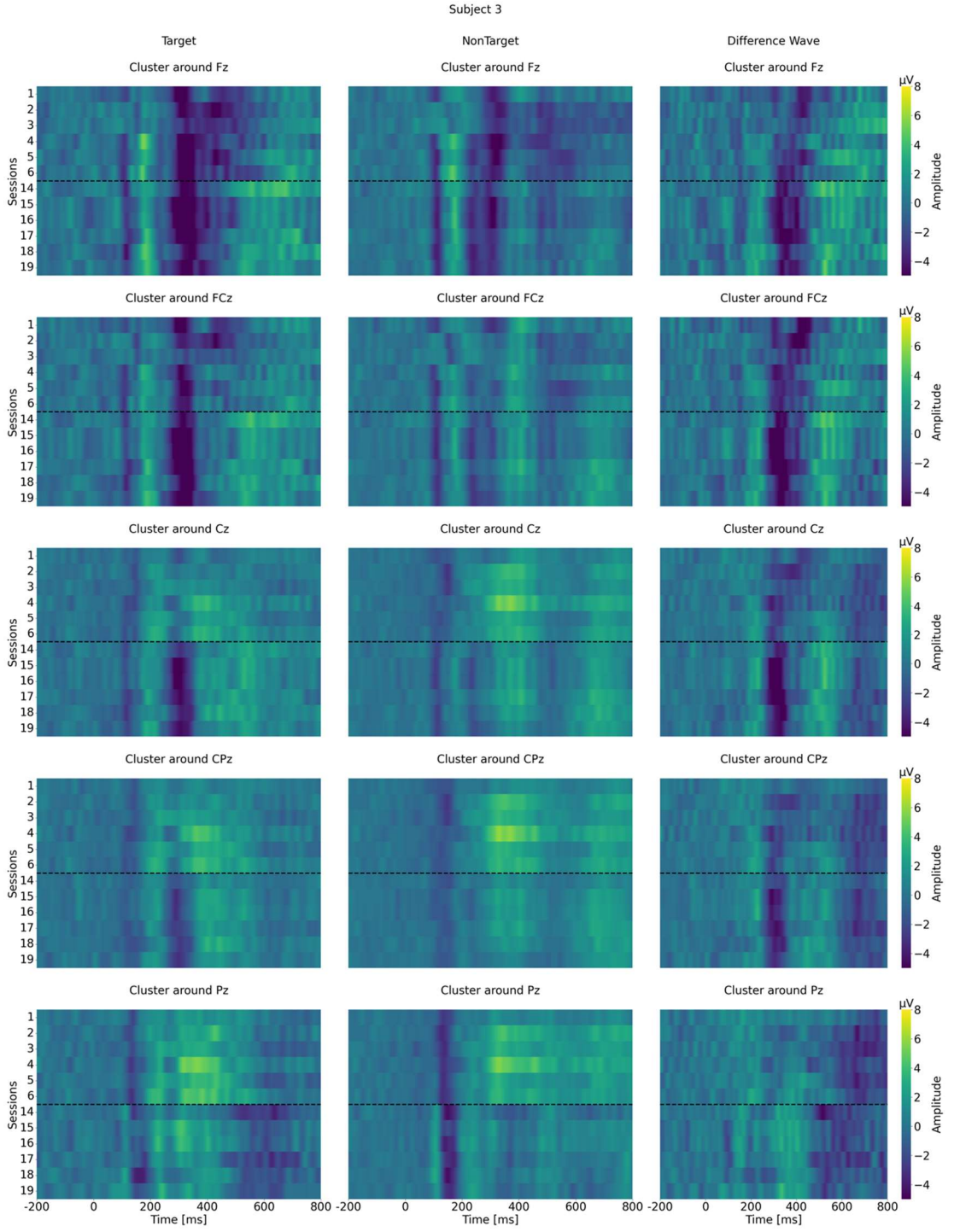


Figure 79: Mean event-related potentials for each session extracted around clusters of interest for Subject 3. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

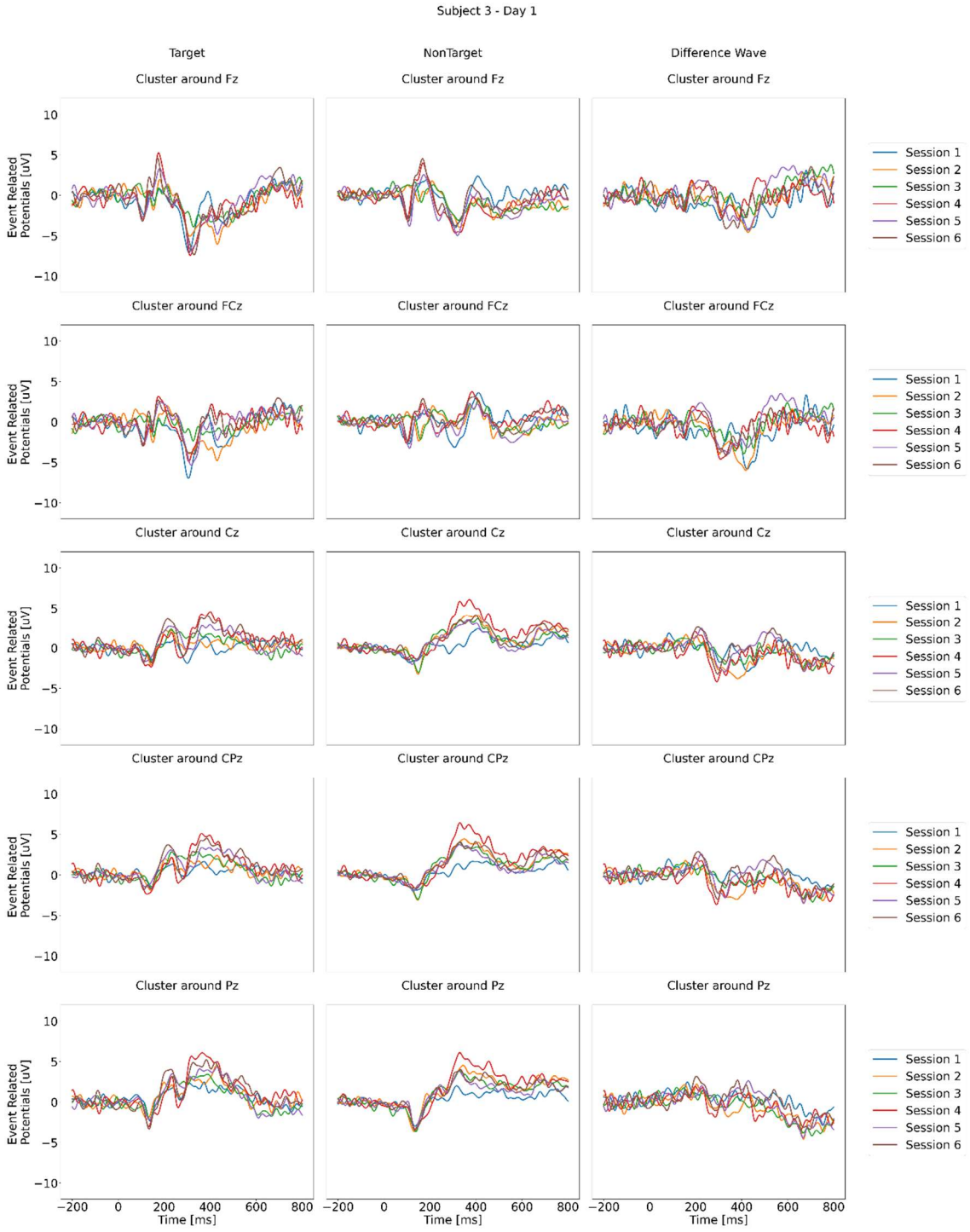


Figure 80: Event Related potentials traces around clusters of electrodes of interest for Subject 3 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

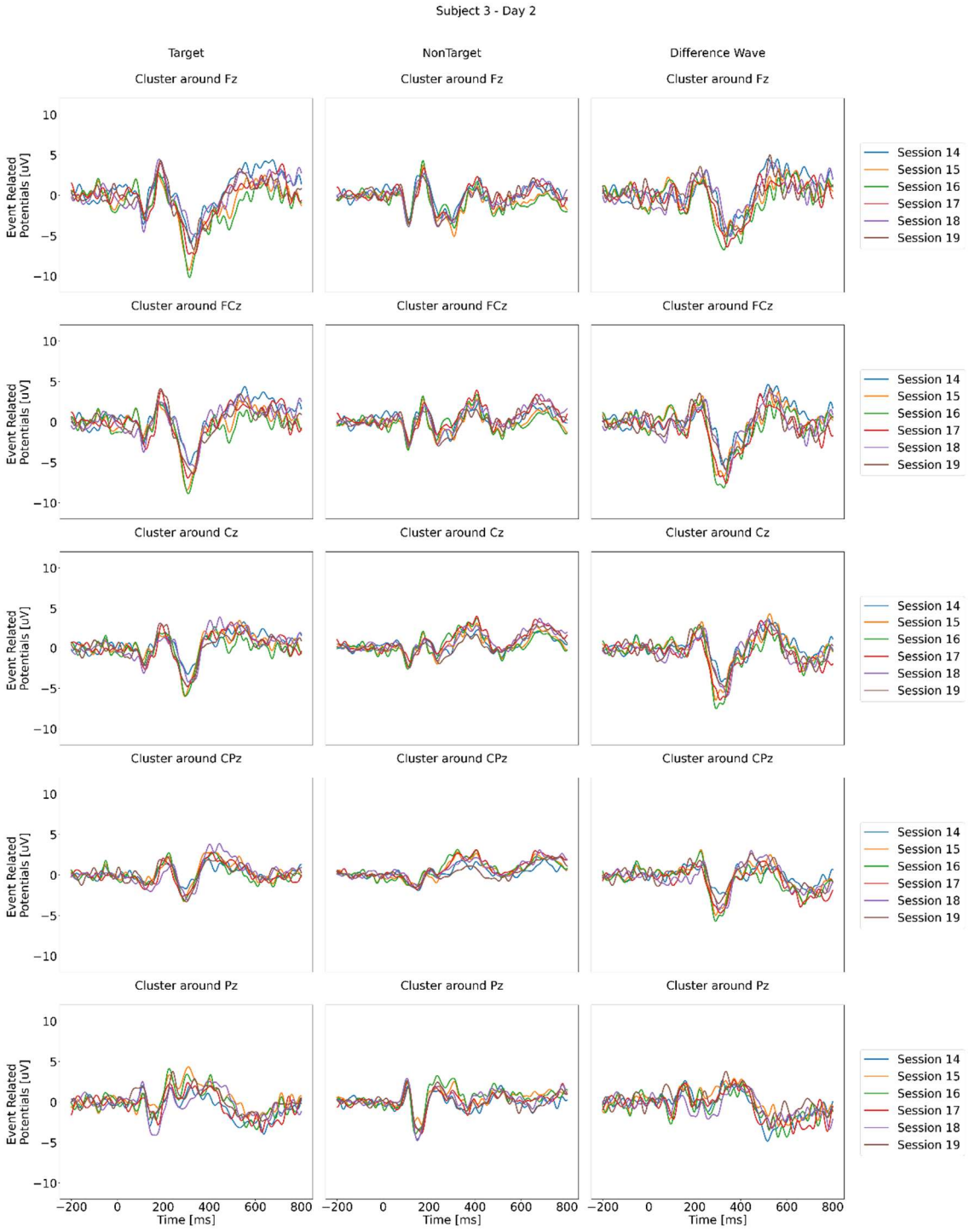


Figure 81: Event Related potentials traces around clusters of electrodes of interest for Subject 3 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

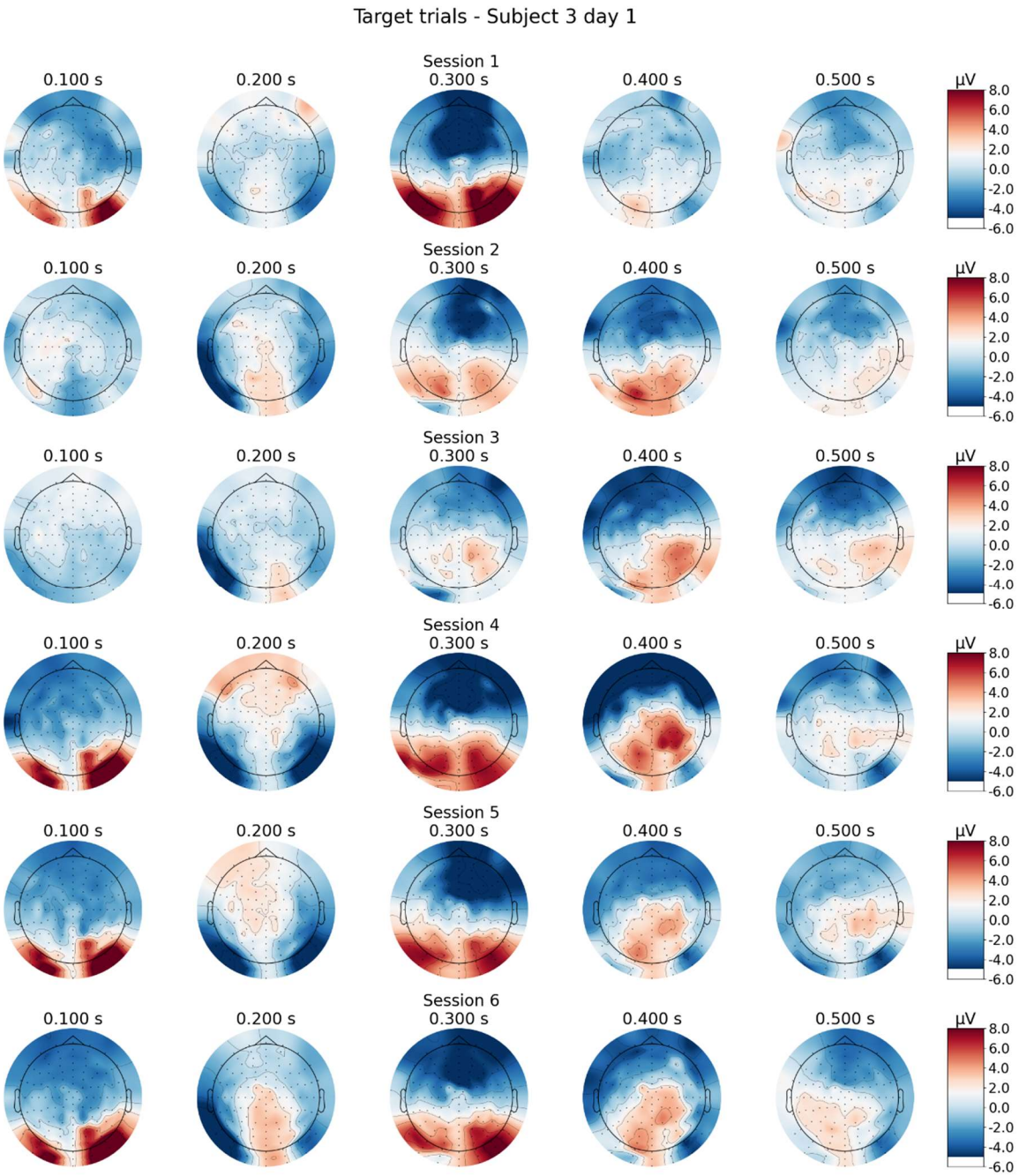


Figure 82: Topographic maps of event related potentials of Subject 3 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

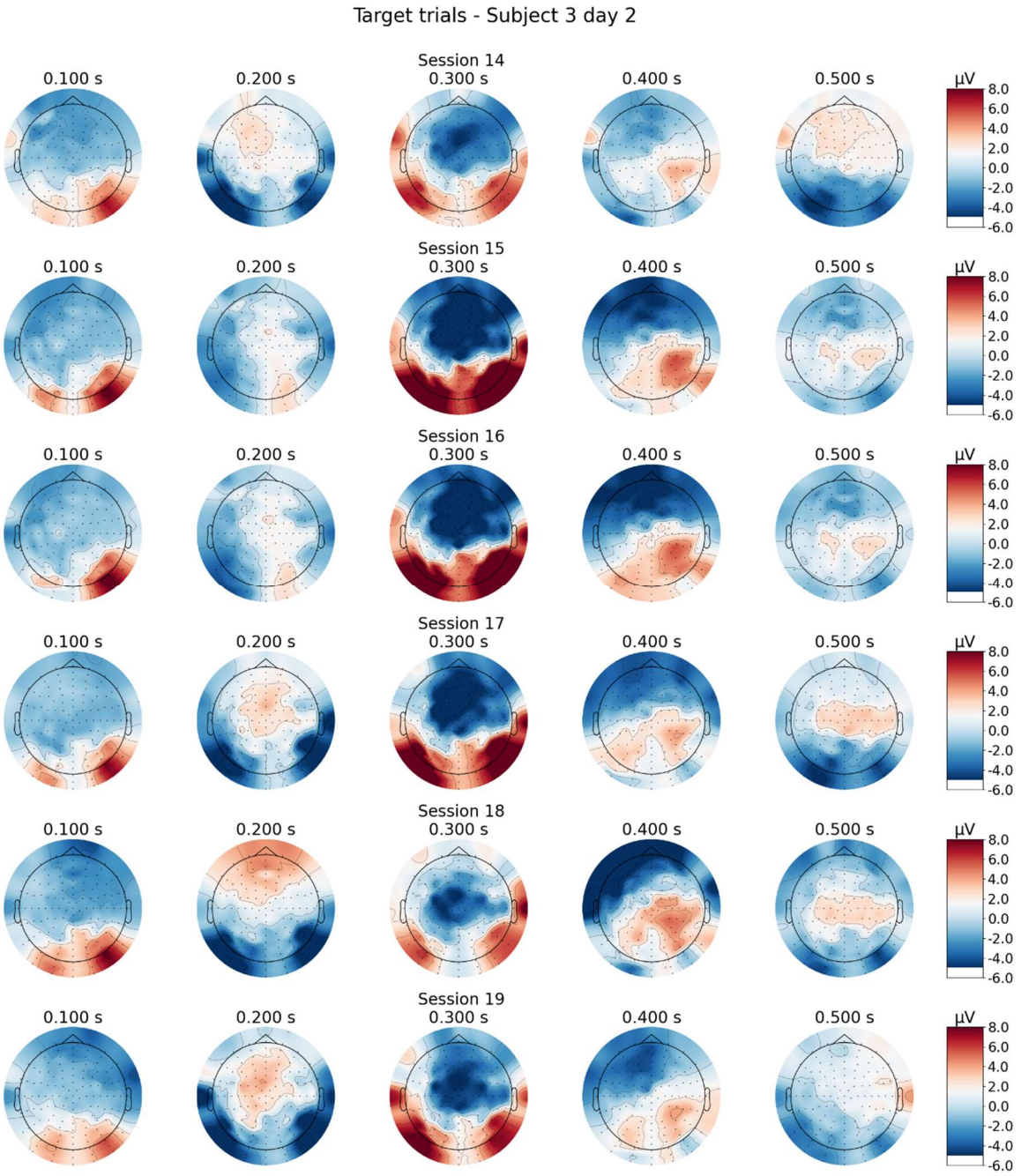


Figure 83: Topographic maps of event related potentials of Subject 3 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

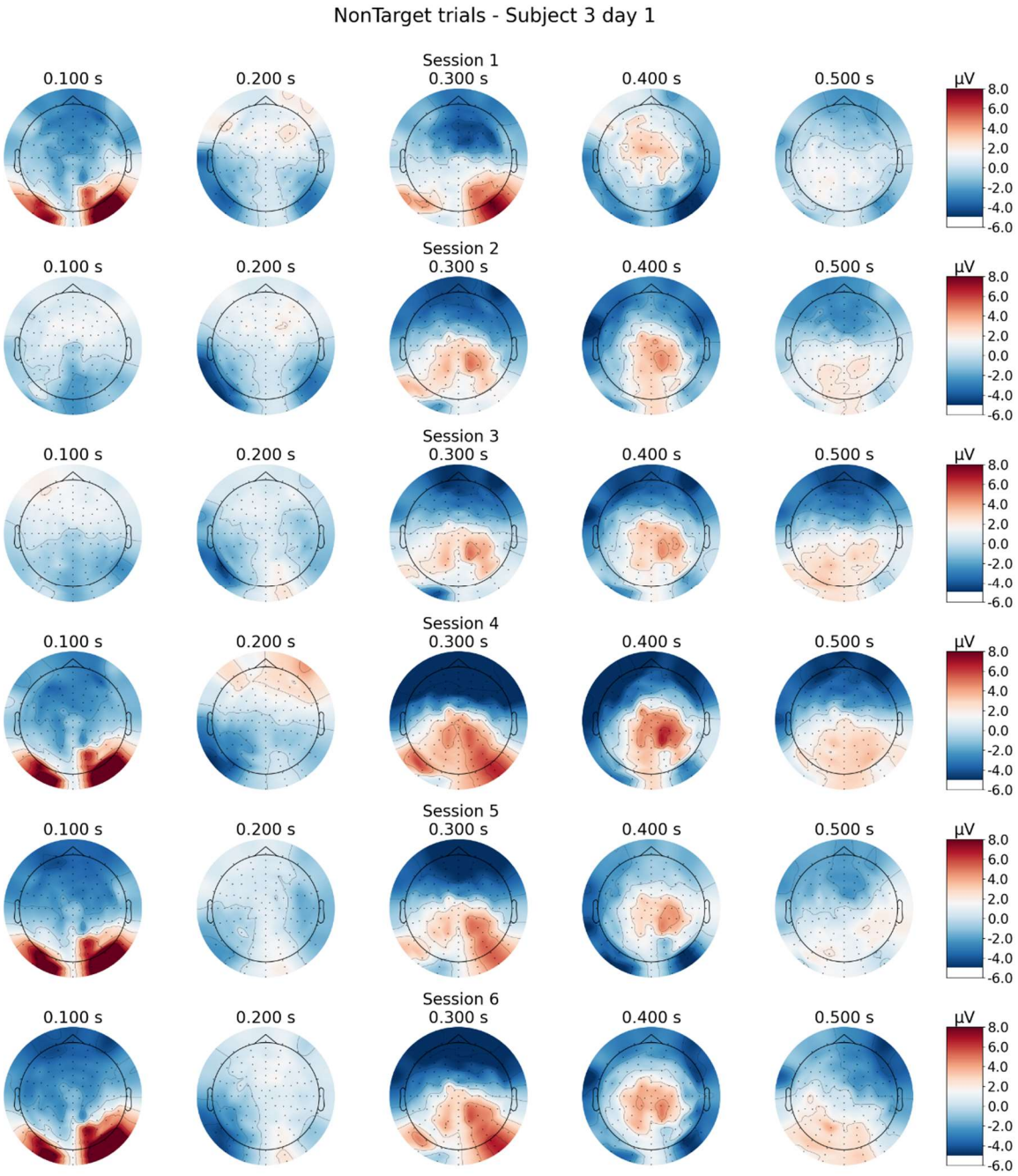


Figure 84: Topographic maps of event related potentials of Subject 3 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

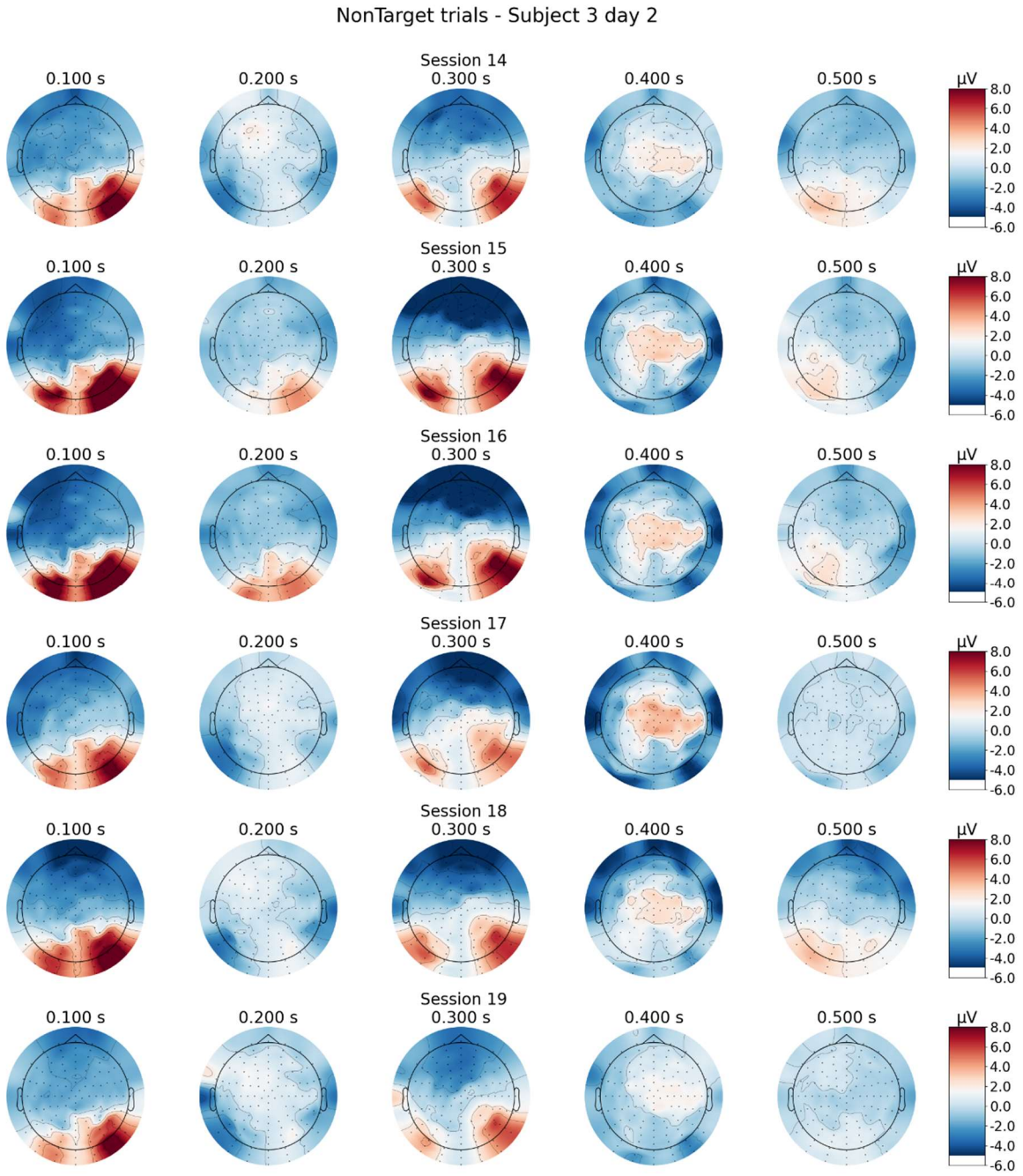


Figure 85: Topographic maps of event related potentials of Subject 3 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.5 Subject 4

Subject 4 was a 24-year-old right-handed male. Their questionnaire revealed that their game strategy did not change during the course of the study. They reported focusing on responding to Target stimuli rather than avoiding Non-Target stimuli. They reported prioritizing speed and accuracy equally. Their mean RT was 295.9ms (SD=11.5ms), mean accuracy to target trials was 100% (SD=0%), and mean accuracy to Non-Target trial was 98.6% (SD=1.8%). Behavioural data from Subject 4 are presented on Figure 86.

5.3.5.1 Questionnaire

	Subject 4
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	Started to guess how many aliens and astronauts were leave (sic), was able to predict if a star was going to show on multiple occasions.
If so, would you be able to say when?	Probably second day of doing them at home
Did any of the game features (such as points or bonus stars) impact your game strategy?	Yes, would prioritise the stars as they were worth 1000 points if you got them straight away where the aliens where only worth 300 and not shooting astronauts were not worth much.
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	No
Did you prioritize speed and accuracy equally?	Yes

Table 23: Questionnaire data from Subject 4.

5.3.5.2 Behavioural analysis

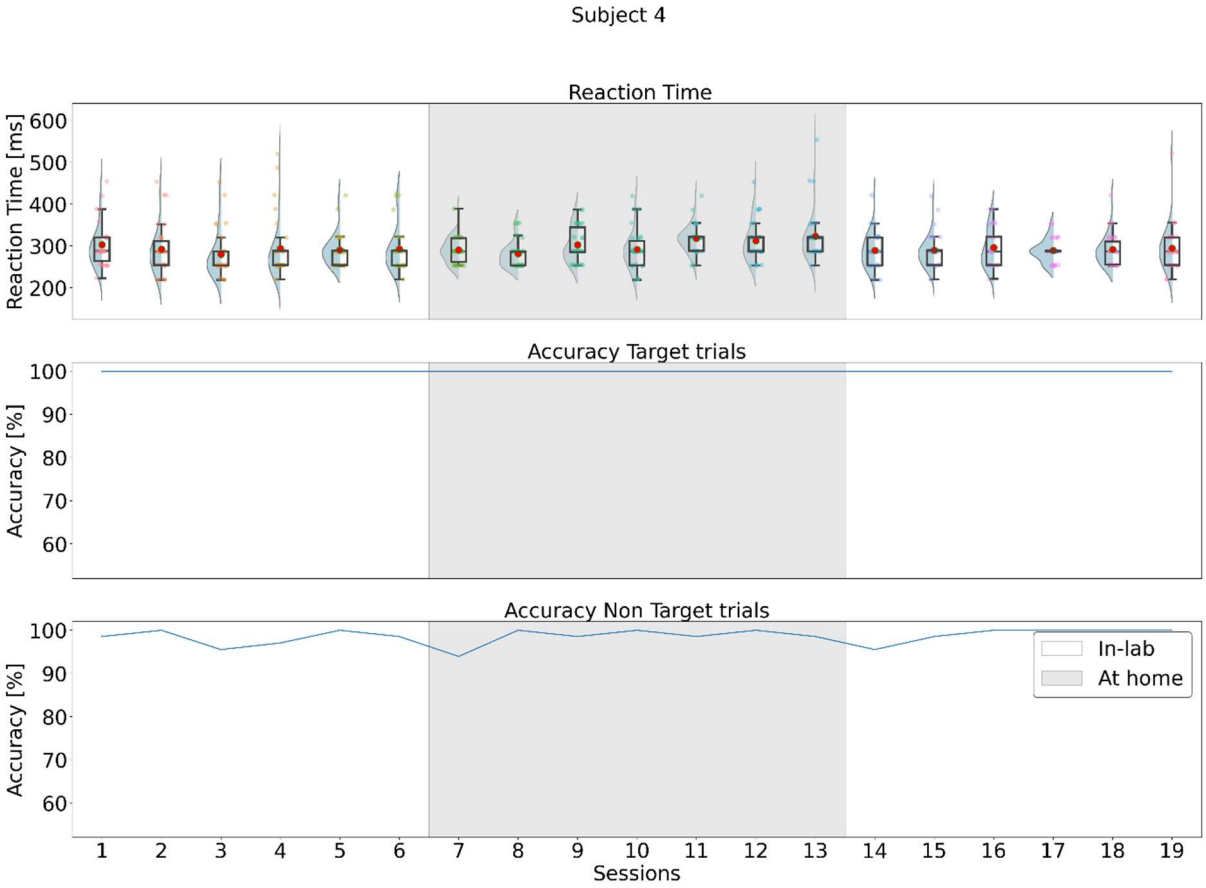


Figure 86: Behavioural responses of Subject 4. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.5.3 EEG analysis

EEG data of Subject 4 are presented on Figures 87 to 93. Both for Target and Non-Target trials, the typical positive deflection of the P300 can be observed around 300ms post stimulus presentation; just after early sensory perceptual components happening between 0 to 250ms. The topography of the signals seems to be consistent within conditions with Target signals peaking around centro-parietal regions and Non-Target trials peaking around fronto-central regions. The amplitudes of the P300 extracted from Non-Target trials are larger than the ones extracted from Target trials as demonstrated by the negative the difference waves presented in Figures 88 and 89. When examining the ERP image (Figure 87) and the topographic maps (Figures 90 to 93), it looks like the amplitudes of the Target and Non-Target signals are stable within days but maybe a bit smaller on the second testing day compared to the first one.

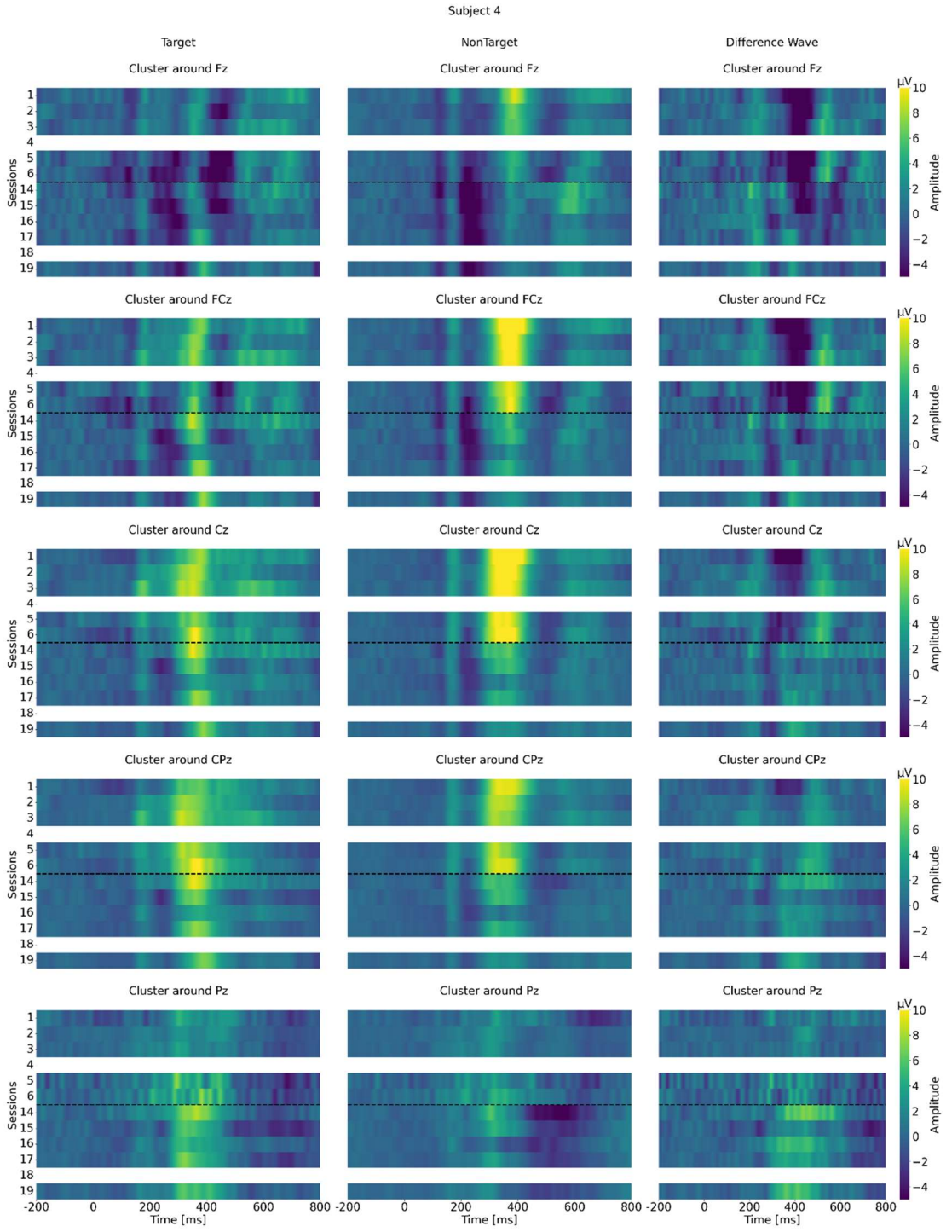


Figure 87: Mean event-related potentials for each session extracted around clusters of interest for Subject 4. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

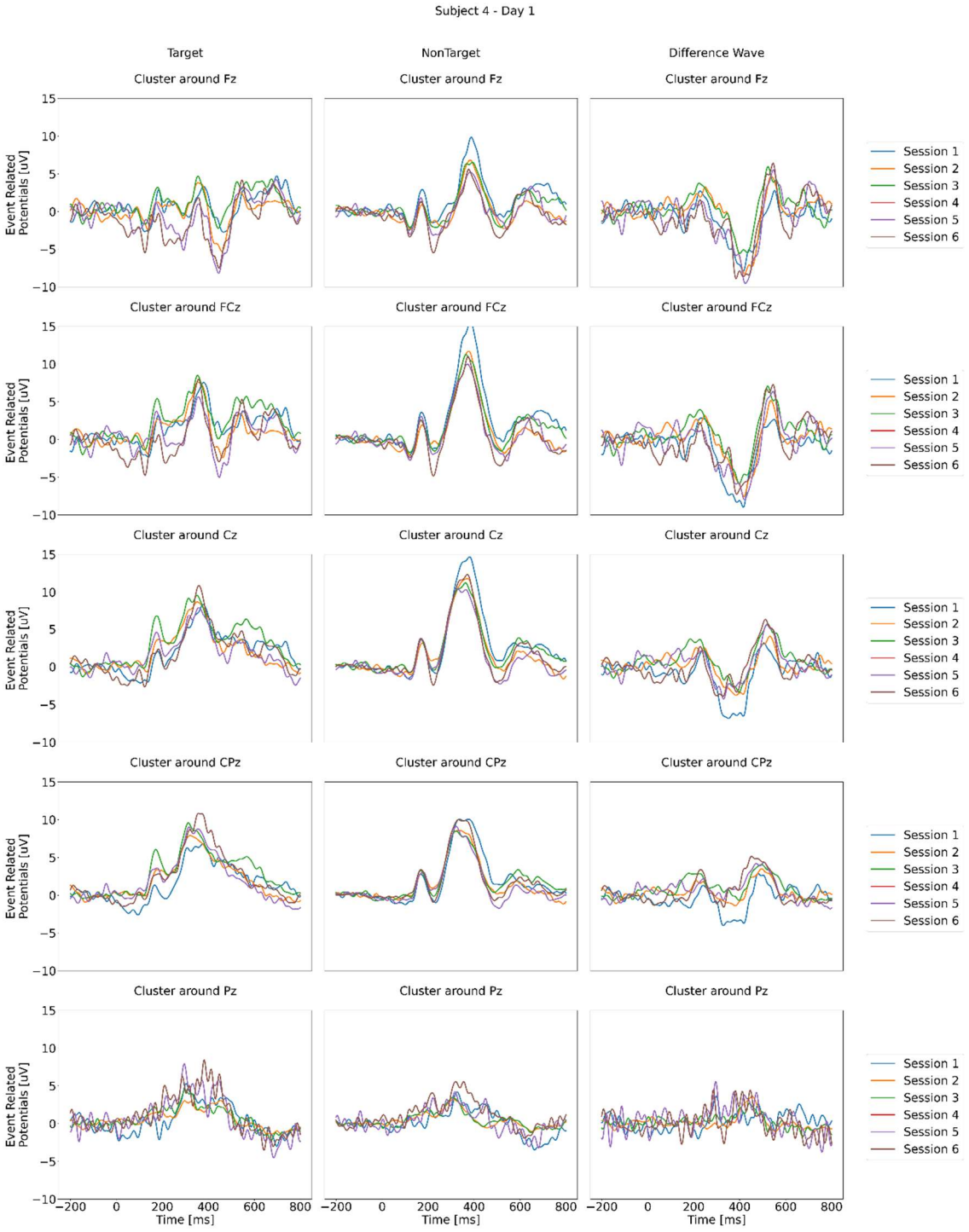


Figure 88: Event Related potentials traces around clusters of electrodes of interest for Subject 4 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

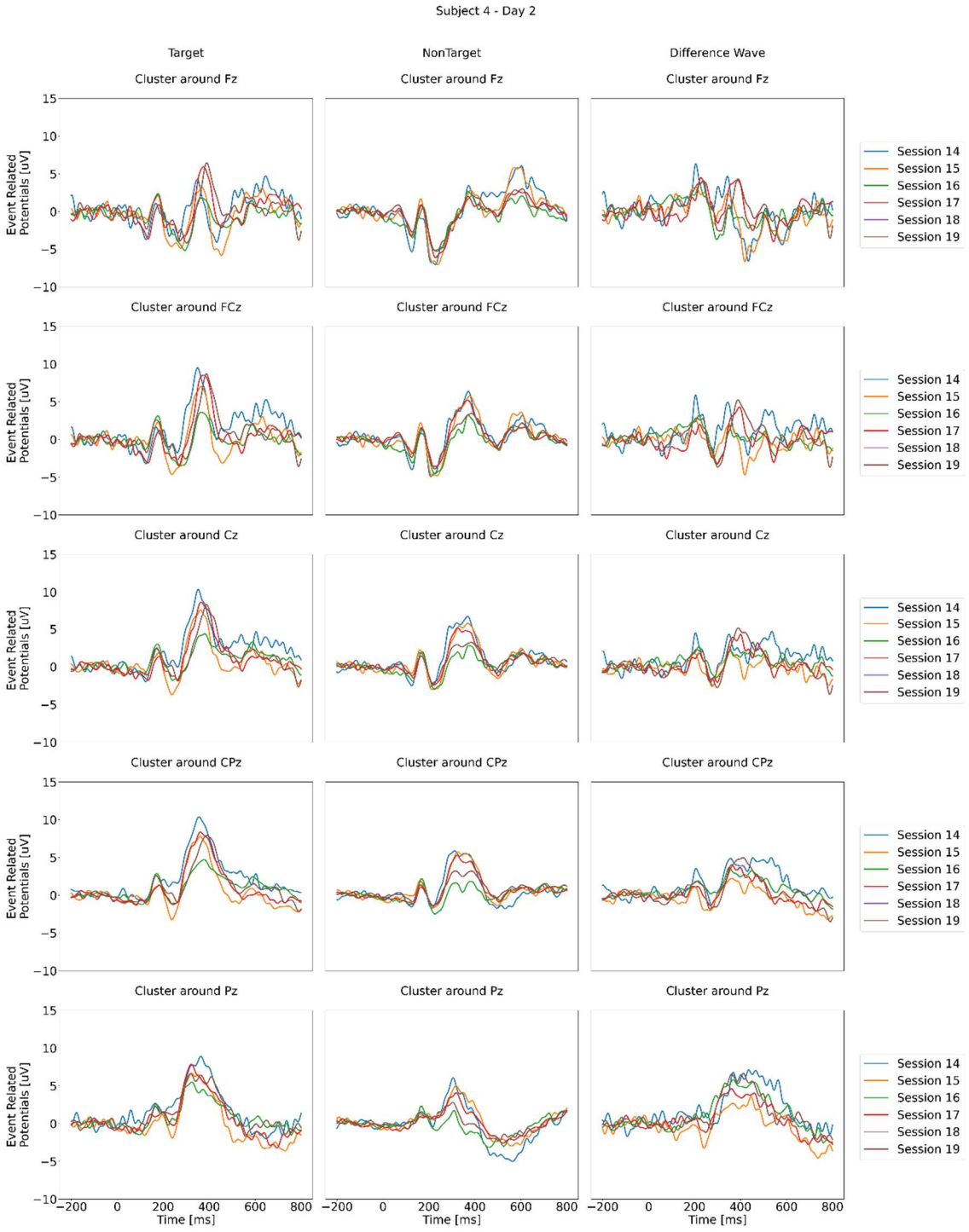


Figure 89: Event Related potentials traces around clusters of electrodes of interest for Subject 4 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

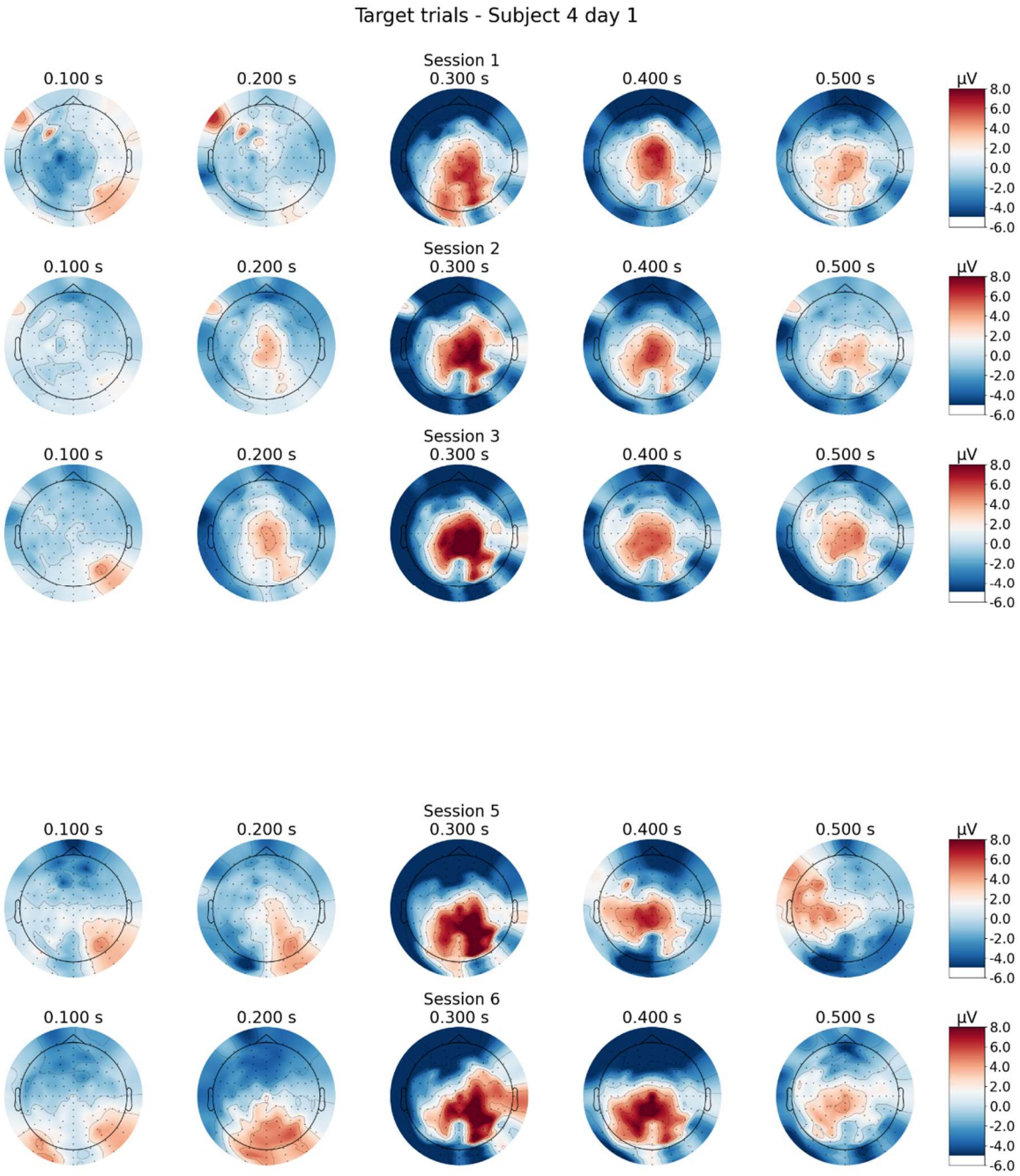


Figure 90: Topographic maps of event related potentials of Subject 4 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

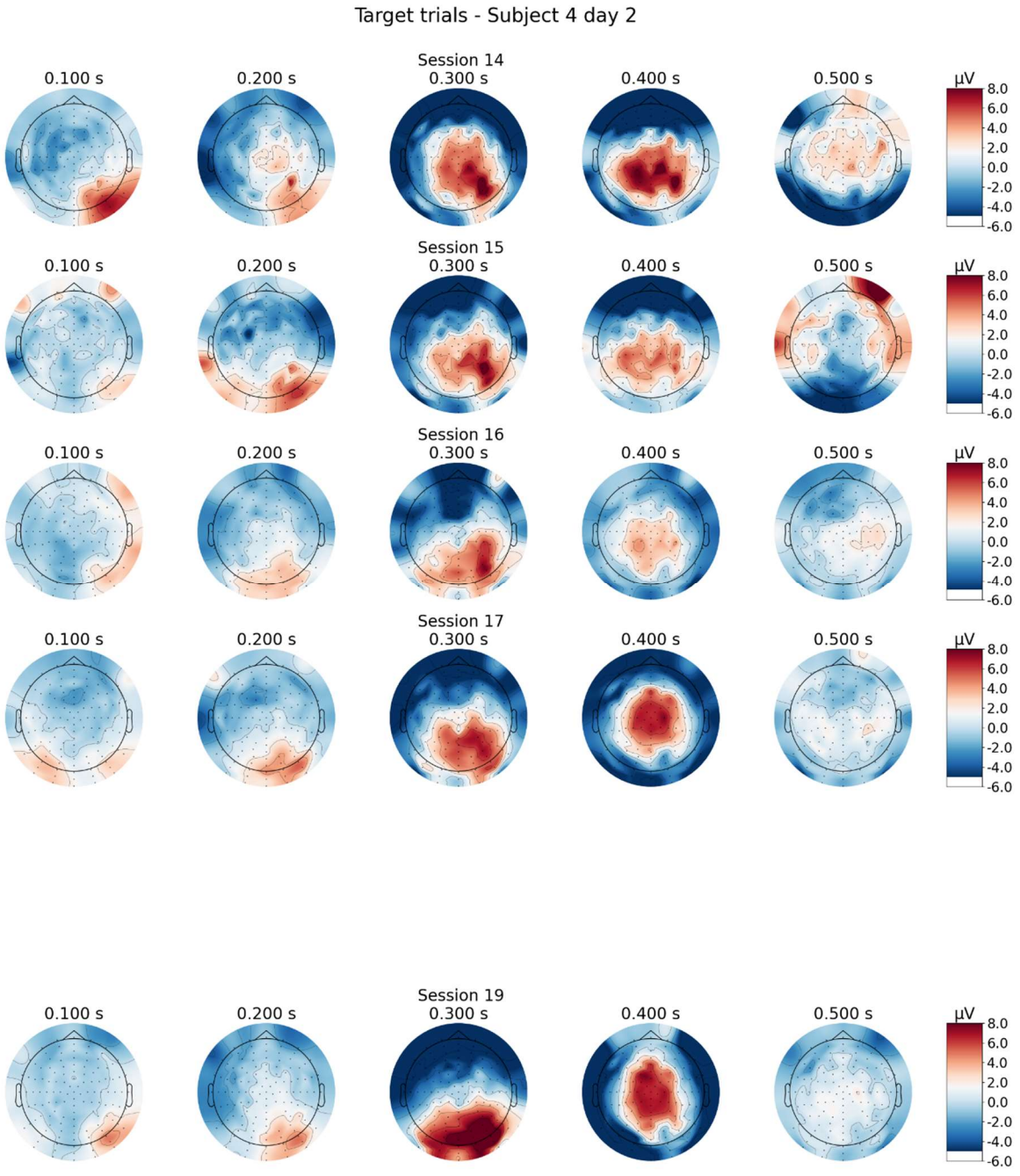


Figure 91: Topographic maps of event related potentials of Subject 4 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

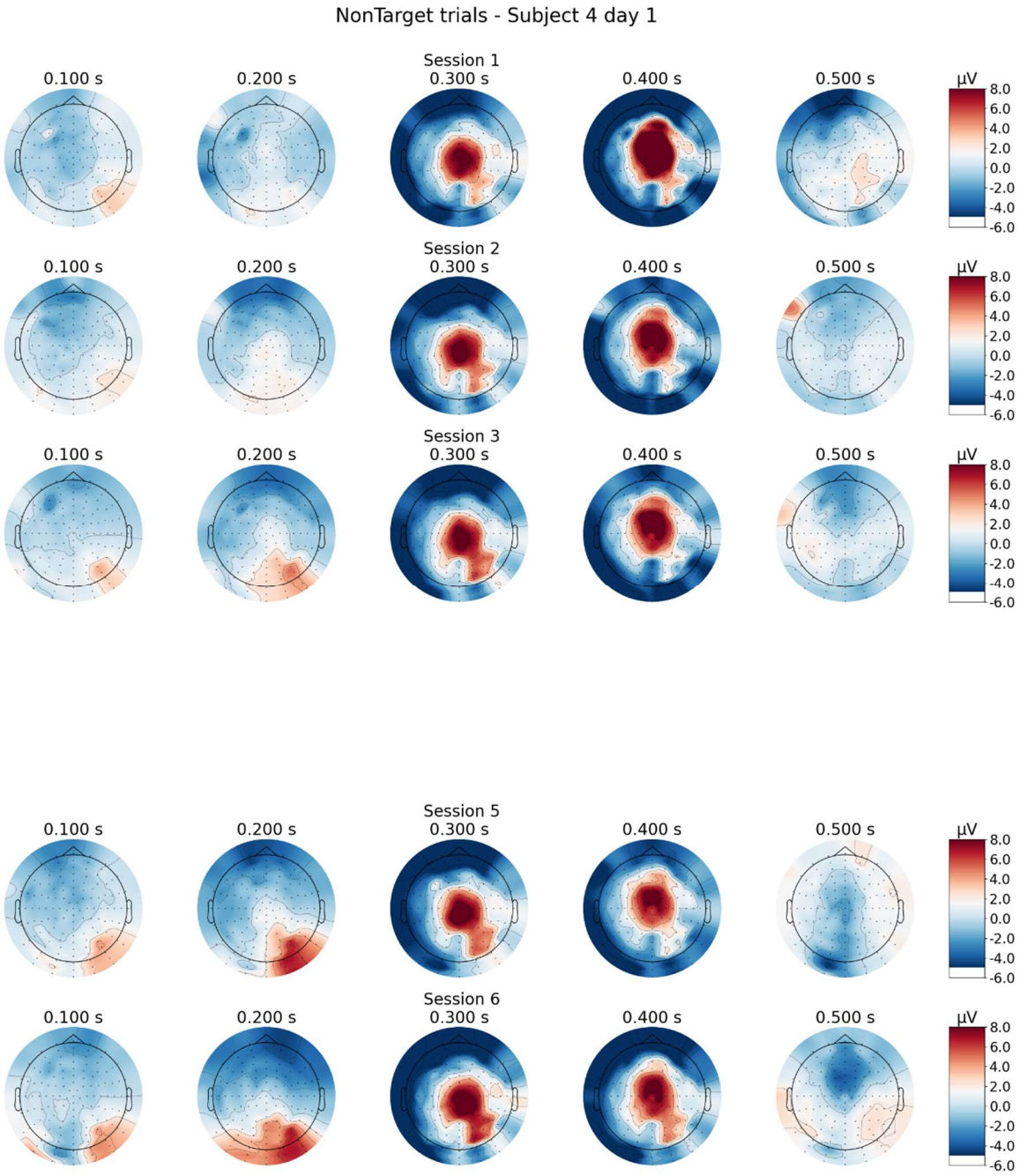


Figure 92: Topographic maps of event related potentials of Subject 4 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

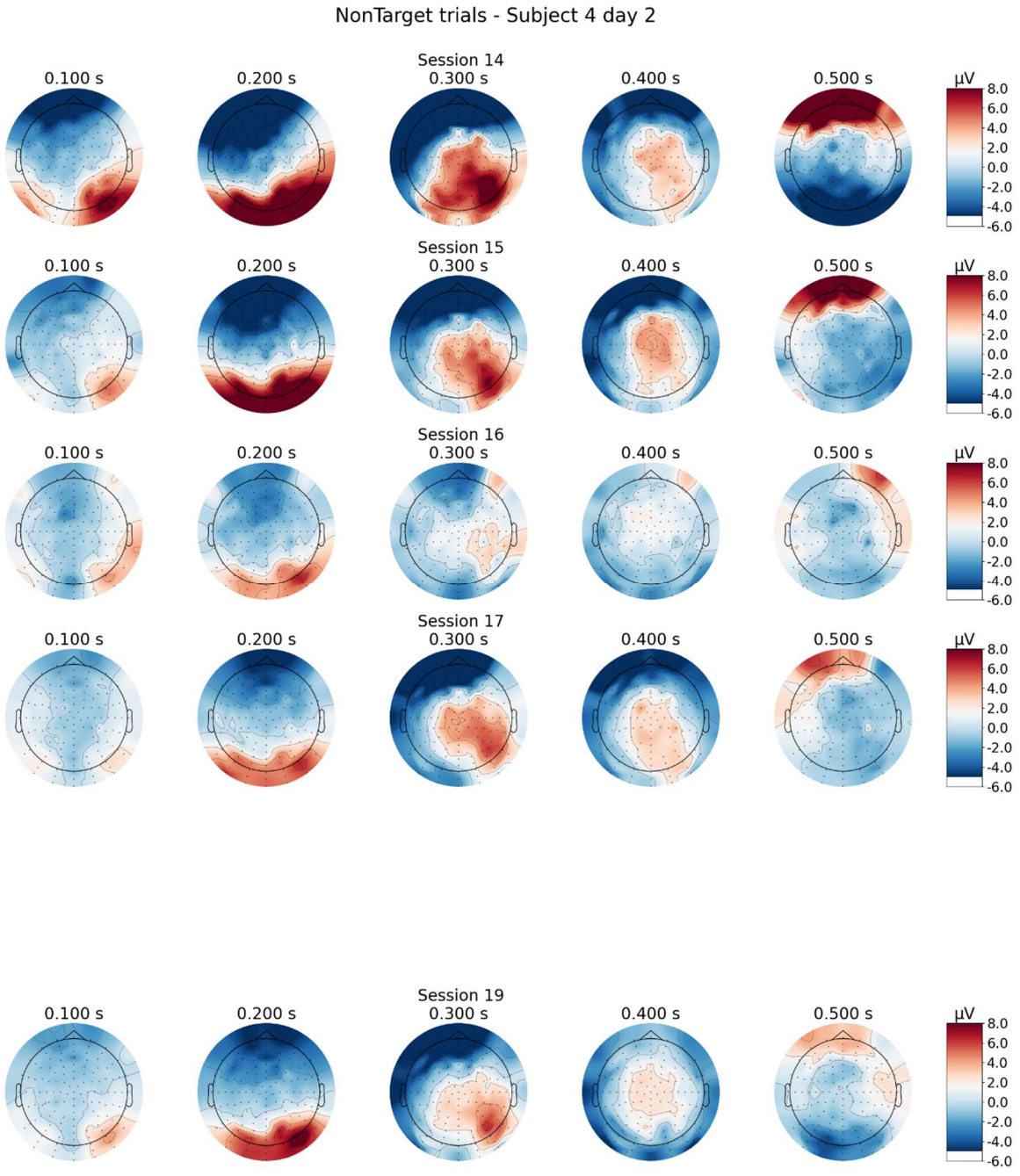


Figure 93: Topographic maps of event related potentials of Subject 4 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.6 Subject 5

Subject 5 was a 33-year-old right-handed male. Their questionnaire revealed that their game strategy did not change during the course of the study. They reported focusing on responding to Target stimuli rather than avoiding Non-Target stimuli. They reported prioritizing accuracy over speed. Their mean RT was 294.2ms (SD=17.9ms), mean accuracy to target trials was 99.6% (SD=1.1%), and mean accuracy to Non-Target trial was 98.1% (SD=1.9%). Behavioural data from Subject 5 are presented on Figure 94.

5.3.6.1 Questionnaire

	Subject 5
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	No
If so, would you be able to say when?	N/A
Did any of the game features (such as points or bonus stars) impact your game strategy?	Greater downside for being wrong than being slow.
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	Yes
Did you prioritize speed and accuracy equally?	No

Table 24: Questionnaire data from Subject 5.

5.3.6.2 Behavioural analysis

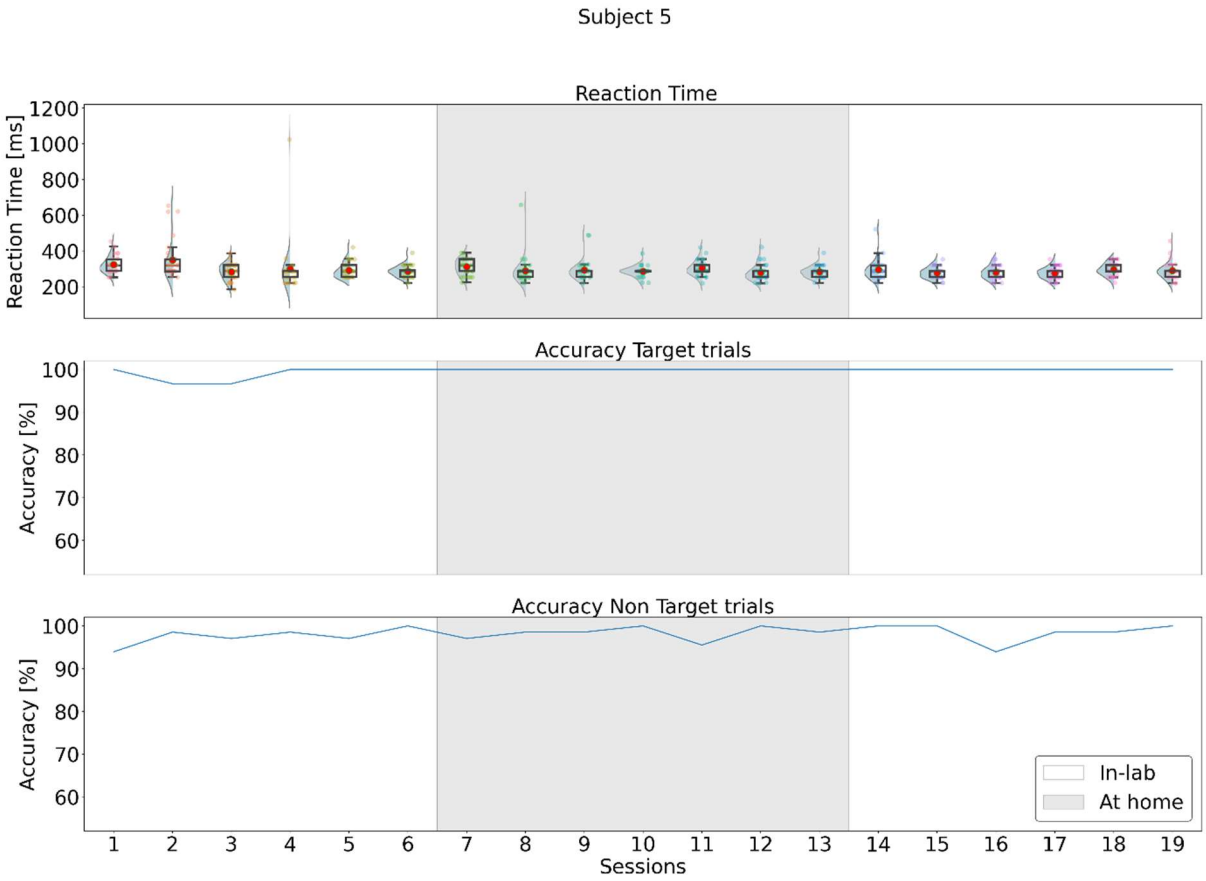


Figure 94: Behavioural responses of Subject 5. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.6.3 EEG analysis

EEG data of Subject 5 are presented on Figures 95 to 101. Both for Target and Non-Target trials, the typical positive deflection of the P300 can be observed around 300 ms post stimulus presentation; just after early sensory perceptual components happening between 0 to 250ms. The topography of the signals seems to be consistent within conditions with Target signals peaking around centro-parietal regions and Non-Target trials peaking around fronto-central regions. The amplitudes of the P300 extracted from Non-Target trials are larger than the ones extracted from Target trials at the clusters of electrodes around Fz, FCz, and Cz as demonstrated by the negative the difference waves presented in Figures 96 and 97. At clusters CPz and Pz, amplitudes of Target P300 are larger compared to the ones of Non-Target P300. When examining the ERP image (Figure 95) and the topographic maps (Figures 98 to 101), it is difficult to discern a clear pattern of amplitude modulation across time for the Target condition. Non-Target amplitude seems to be decreasing with time.

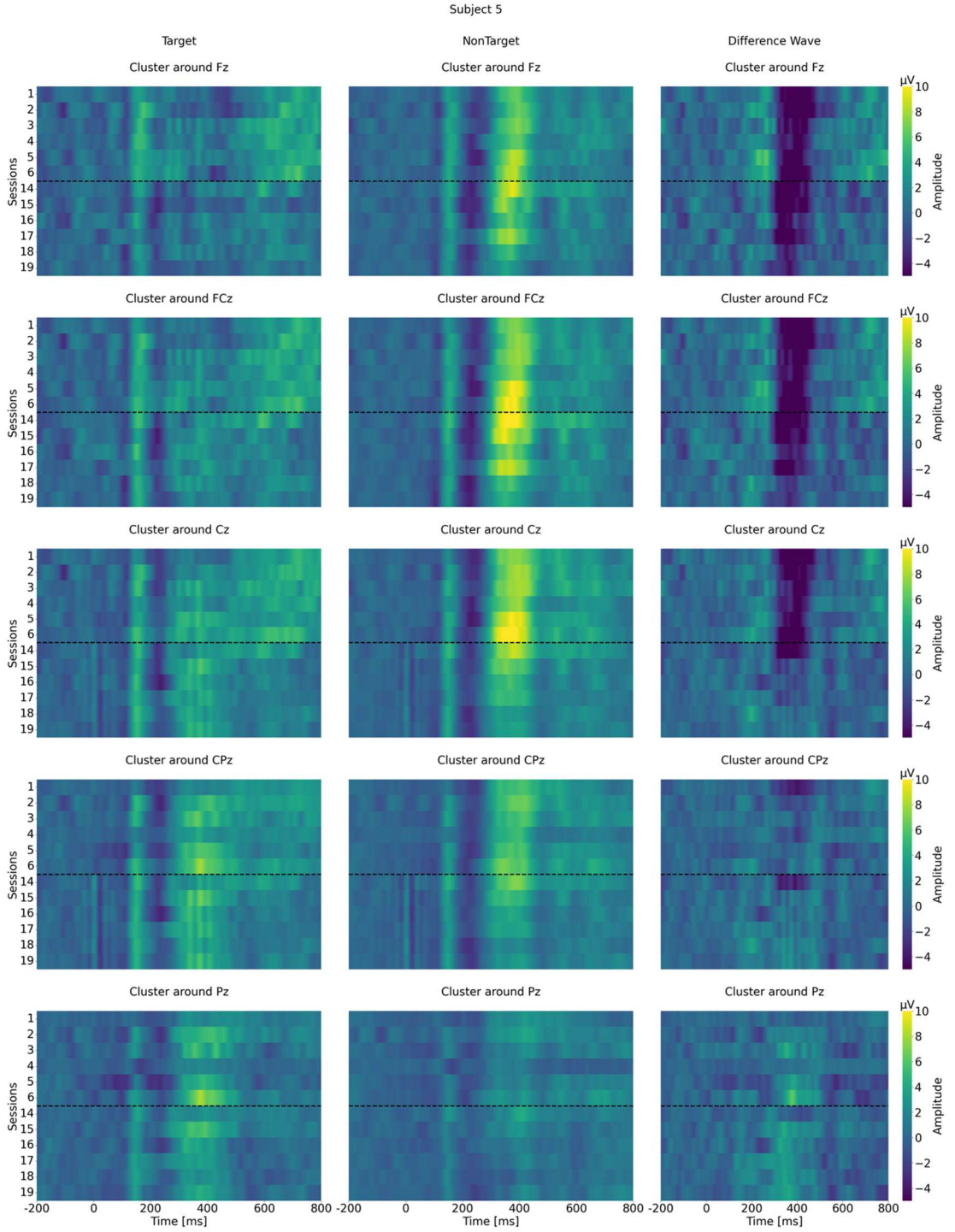


Figure 95: Mean event-related potentials for each session extracted around clusters of interest for Subject 5. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

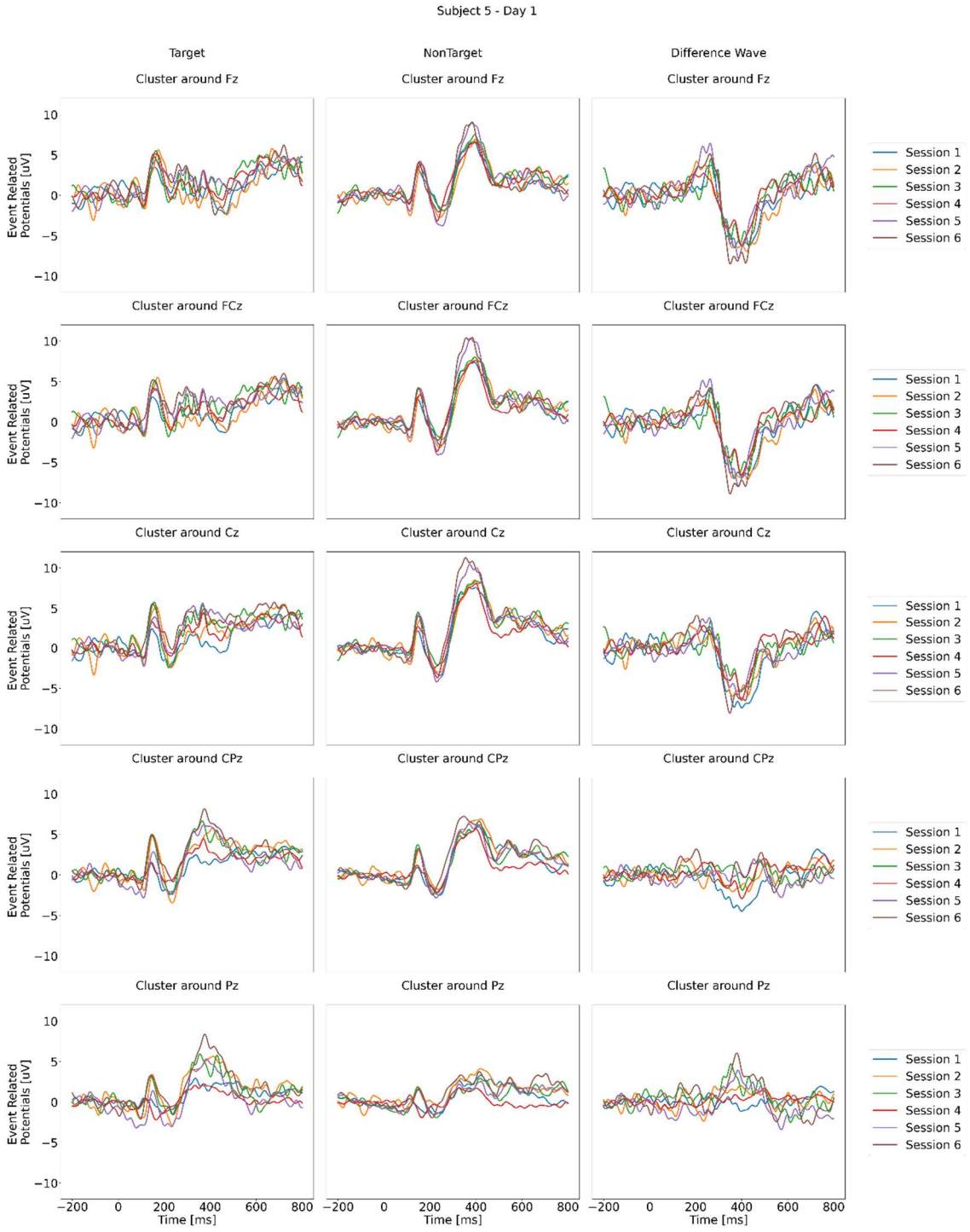


Figure 96: Event Related potentials traces around clusters of electrodes of interest for Subject 5 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

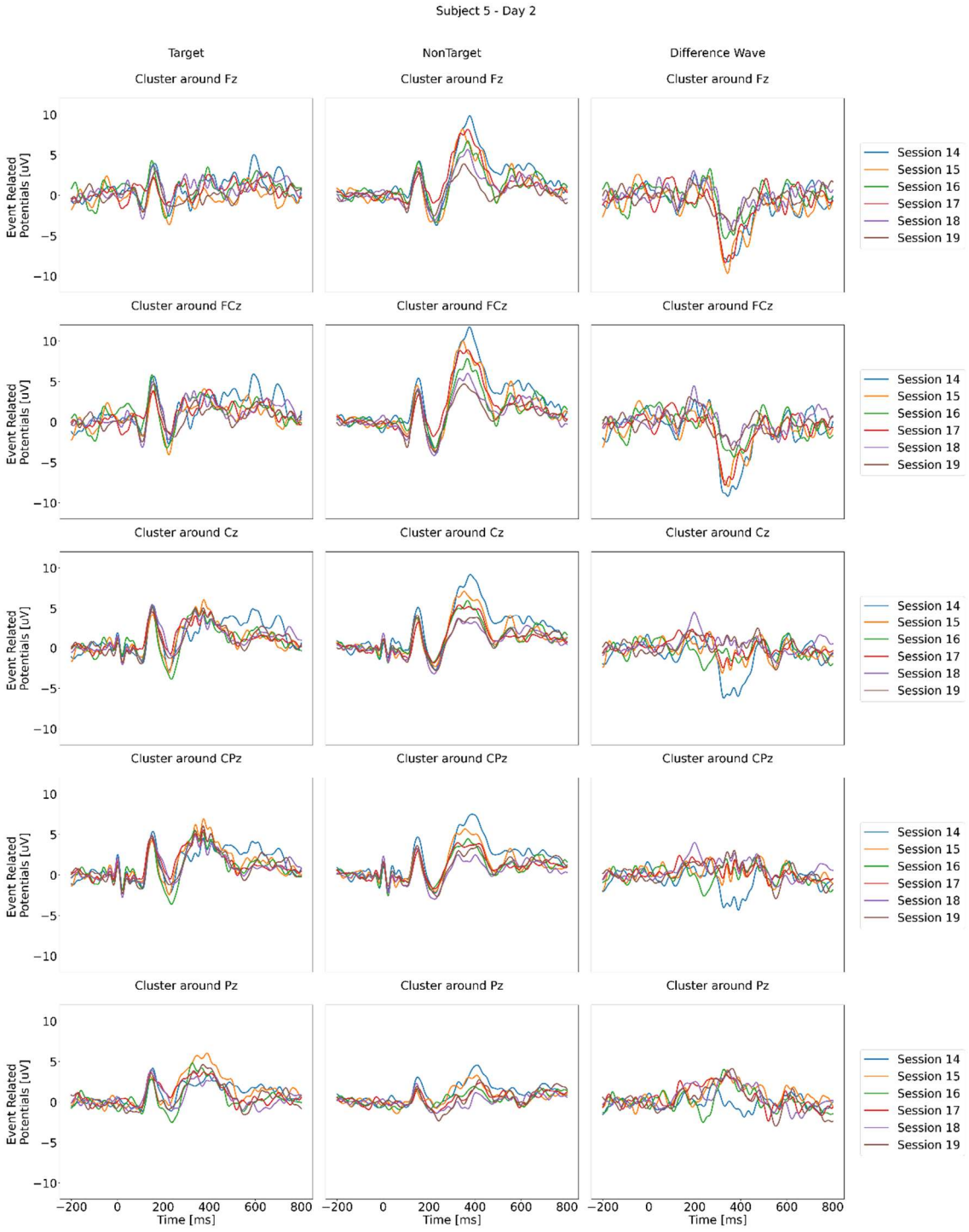


Figure 97: Event Related potentials traces around clusters of electrodes of interest for Subject 5 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

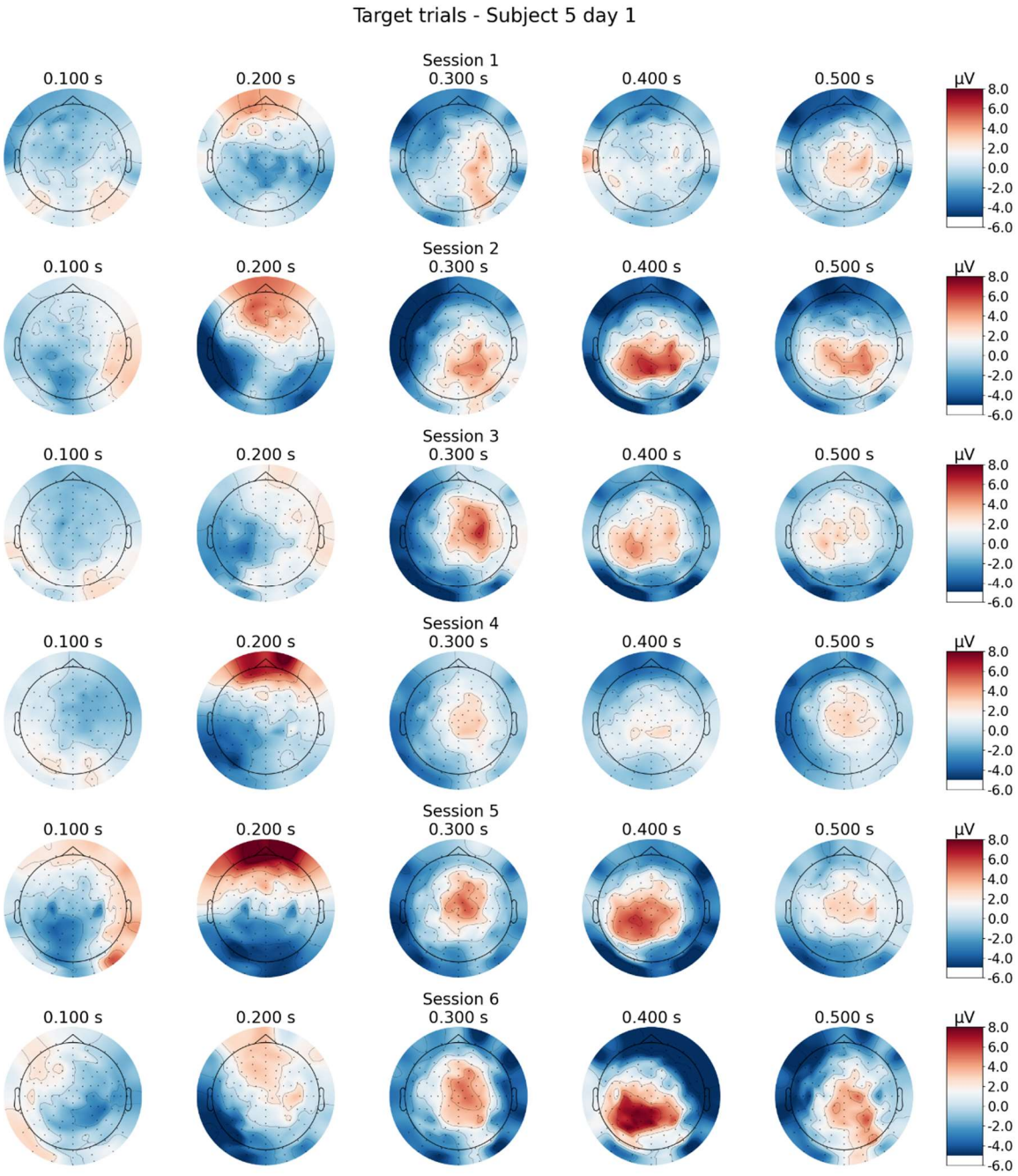


Figure 98: Topographic maps of event related potentials of Subject 5 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

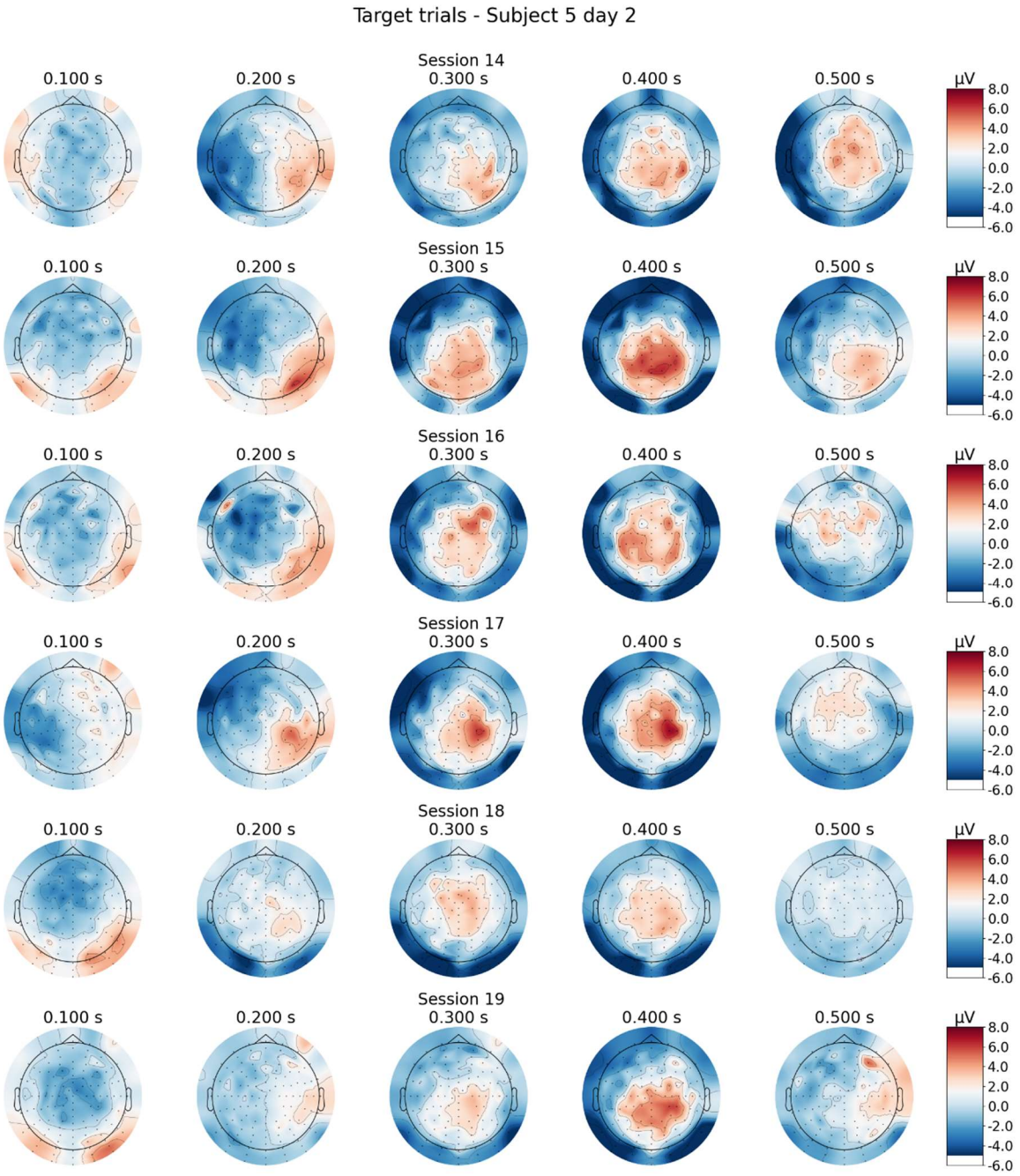


Figure 99: Topographic maps of event related potentials of Subject 5 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

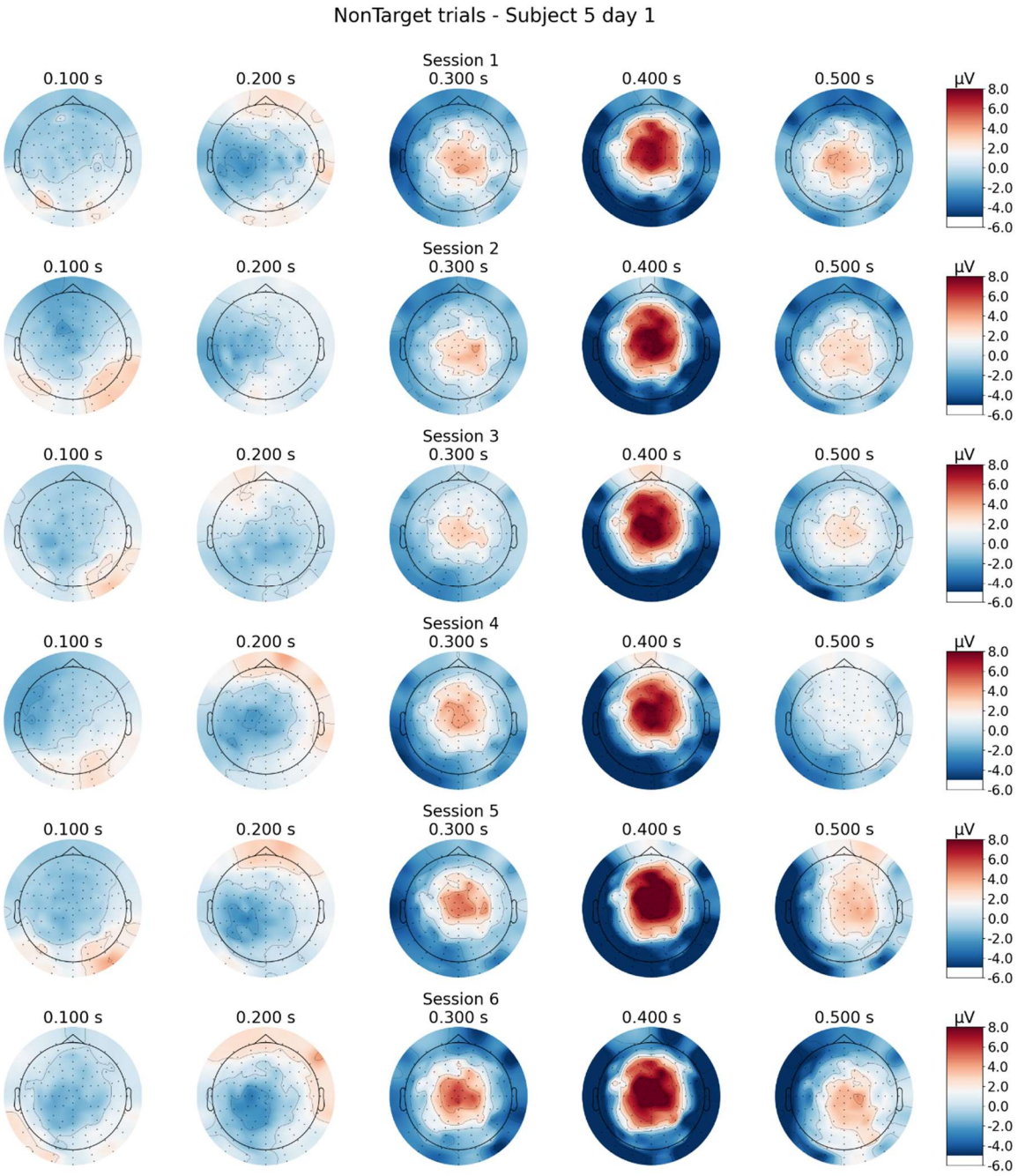


Figure 100: Topographic maps of event related potentials of Subject 5 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

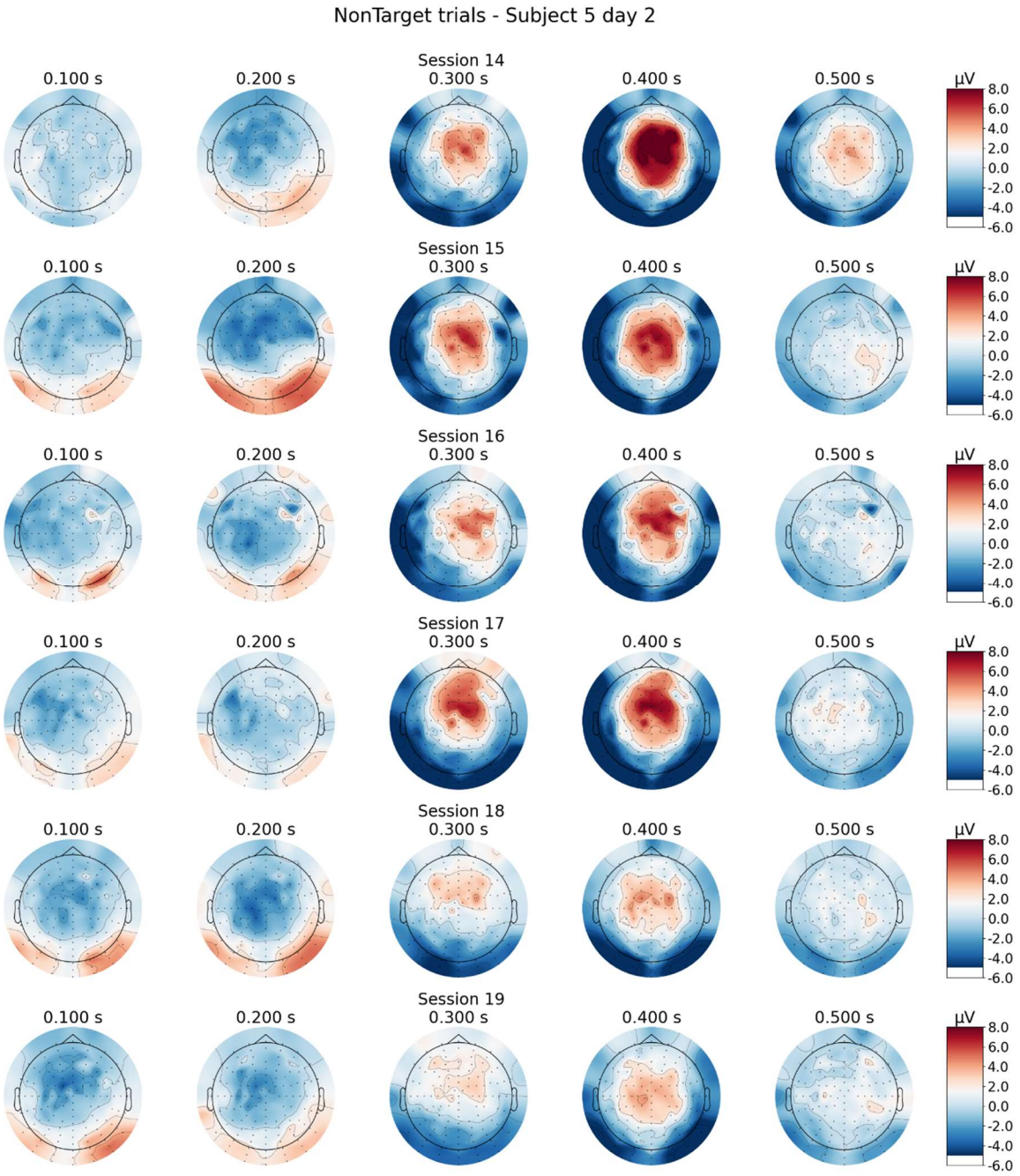


Figure 101: Topographic maps of event related potentials of Subject 5 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.7 Subject 6

Subject 6 was a 25-year-old right-handed female. Their questionnaire revealed that their game strategy did not change during the course of the study. They reported focusing on responding to Target stimuli rather than avoiding Non-Target stimuli. They prioritized accuracy and speed equally. Their mean RT was 336.2ms (SD=10.9ms), mean accuracy to target trials was 99.6% (SD=1.1%), and mean accuracy to Non-Target trial was 99.6% (SD=0.7%). Behavioural data from Subject 6 are presented on Figure 102.

5.3.7.1 Questionnaire

	Subject 6
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	I noticed no change
If so, would you be able to say when?	N/A
Did any of the game features (such as points or bonus stars) impact your game strategy?	Yes, both points and bonus stars mad the game more exciting. You also knew that when you reached a certain number of bonus stars then the level would be complete
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	No
Did you prioritize speed and accuracy equally?	Yes

Table 25: Questionnaire data from Subject 6.

5.3.7.2 Behavioural analysis

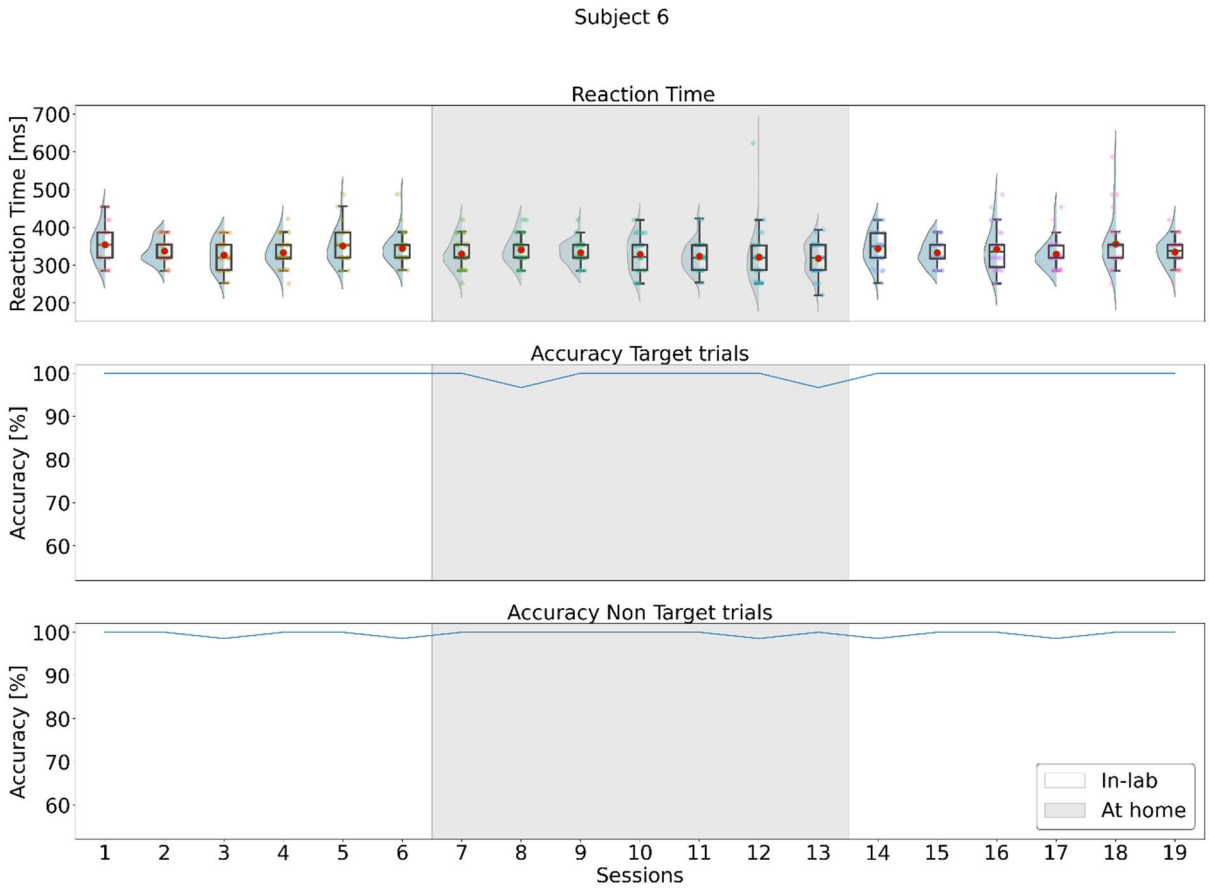


Figure 102: Behavioural responses of Subject 6. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.7.3 EEG analysis

EEG data of Subject 6 are presented on Figures 103 to 109. Both for Target and Non-Target trials, the typical positive deflection of the P300 can be observed around 300 ms post stimulus presentation; just after early sensory perceptual components happening between 0 to 250 ms. The topography of the Non-Target signals seems to be quite consistent and peaks around fronto-central regions. On the other hand, the topography of Target signal seems to be less consistent with peaks around fronto-central regions during the first in-laboratory visit, and peaks both around fronto-central and centro-parietal regions during the second in-laboratory visit. The amplitudes of the P300 extracted from Target and Non-Target trials seem to be around the same level as demonstrated by the very small difference waves presented in Figures 104 and 105. When examining the ERP image (Figure 103), it seems that Non-Target signals could be decreasing across days and sessions. The topography of the Target trial seems to change with time (Figures 106 to 109), moving from fronto-central regions to centro-parietal regions.

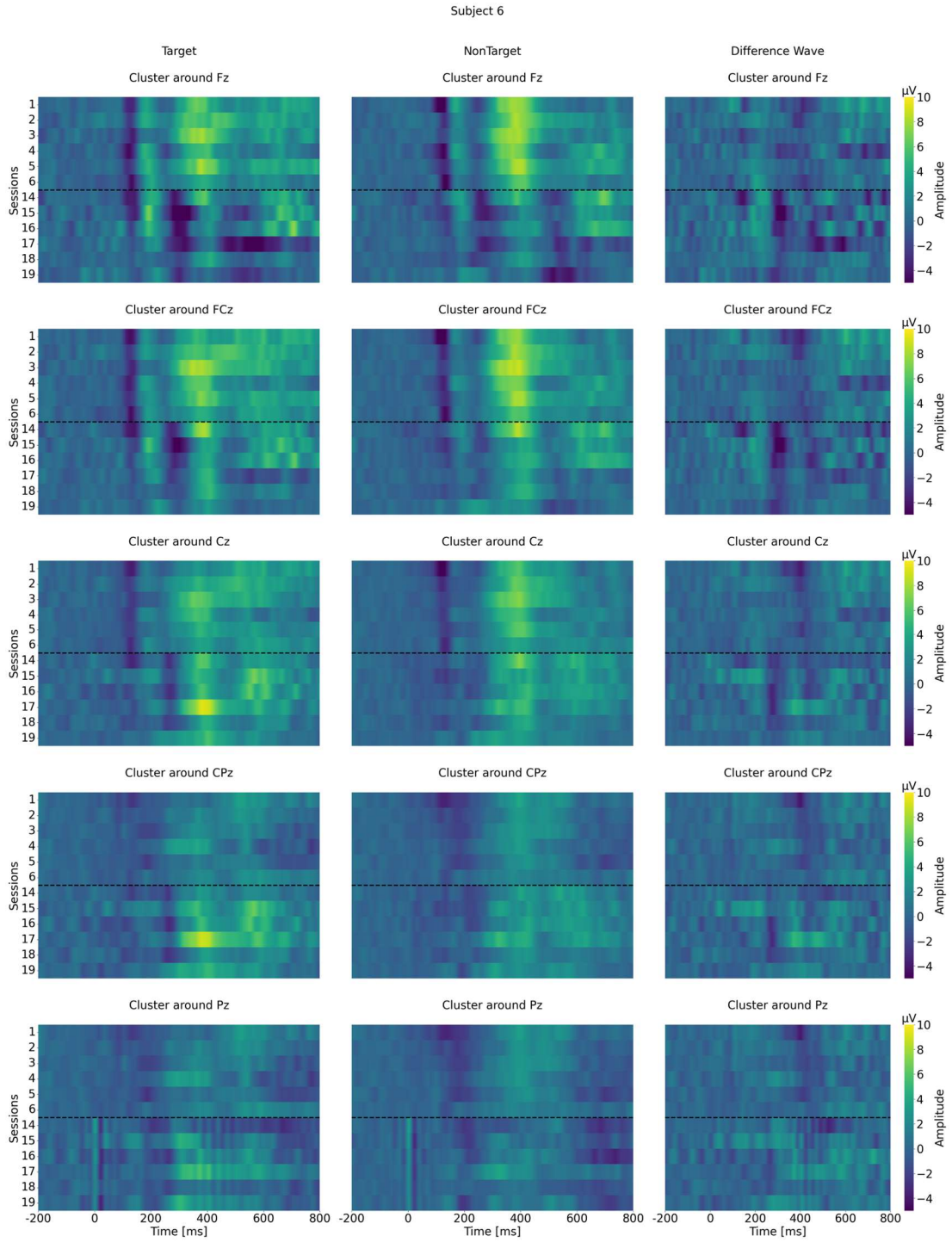


Figure 103: Mean event-related potentials for each session extracted around clusters of interest for Subject 6. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

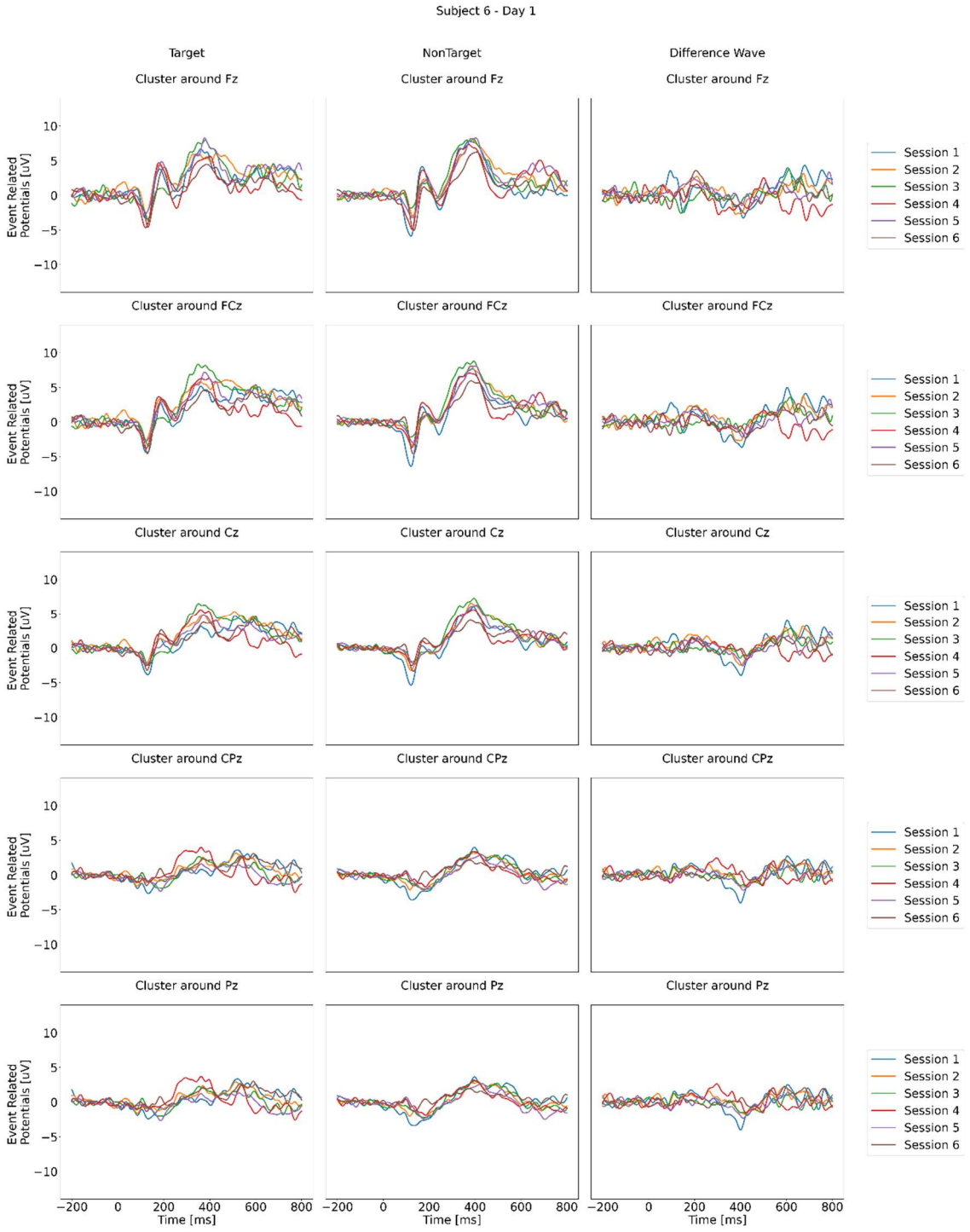


Figure 104: Event Related potentials traces around clusters of electrodes of interest for Subject 6 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

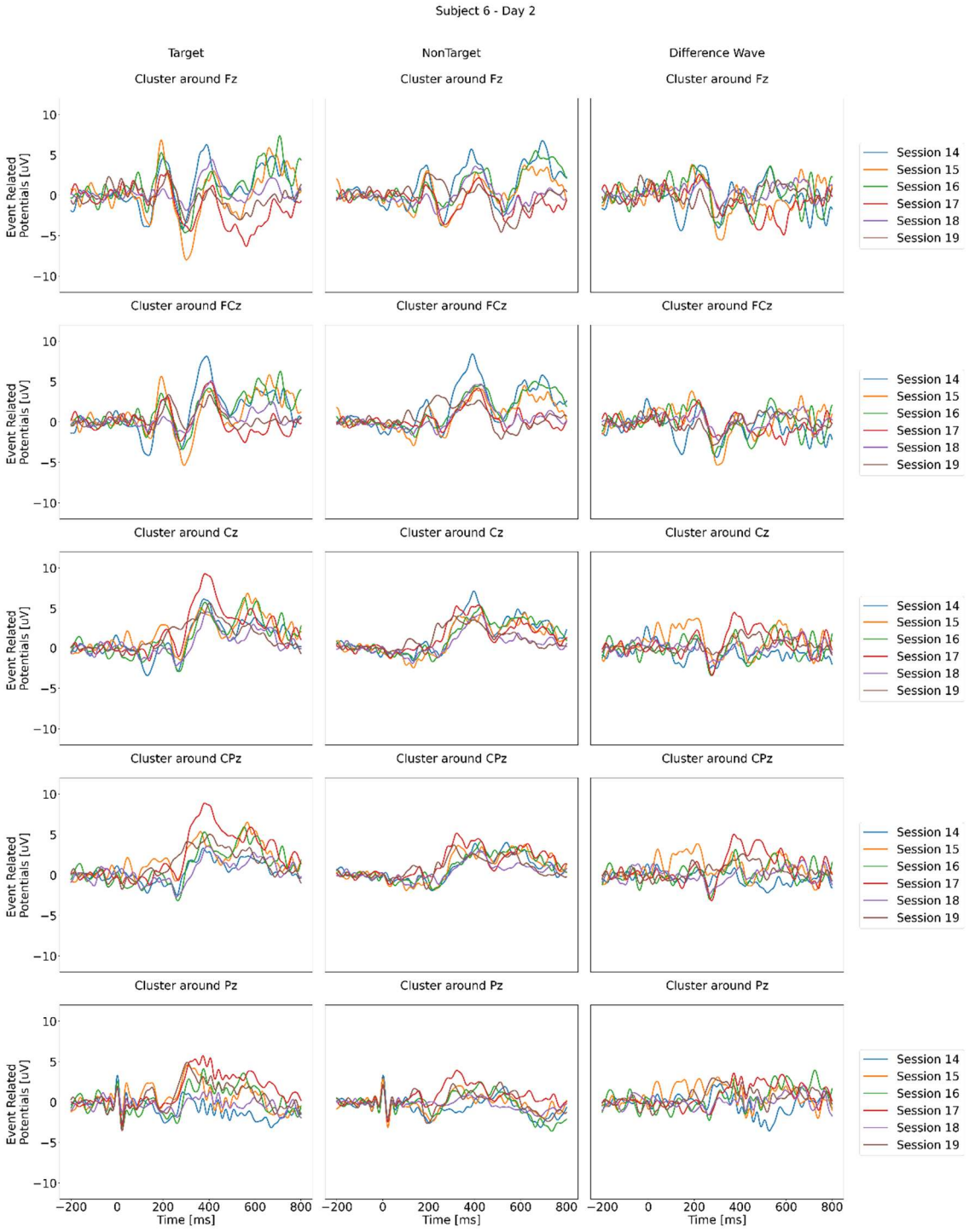


Figure 105: Event Related potentials traces around clusters of electrodes of interest for Subject 6 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

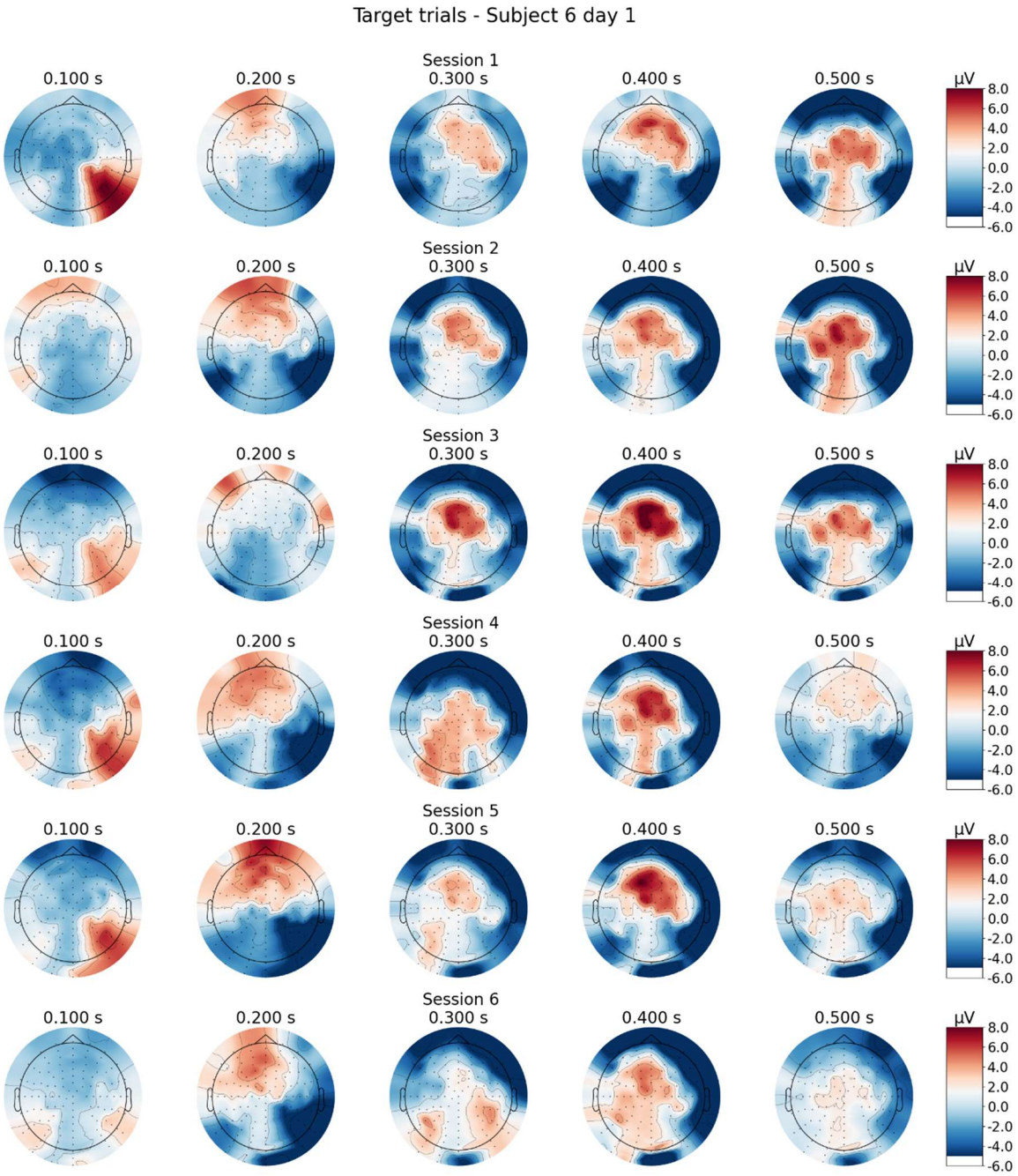


Figure 106: Topographic maps of event related potentials of Subject 6 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

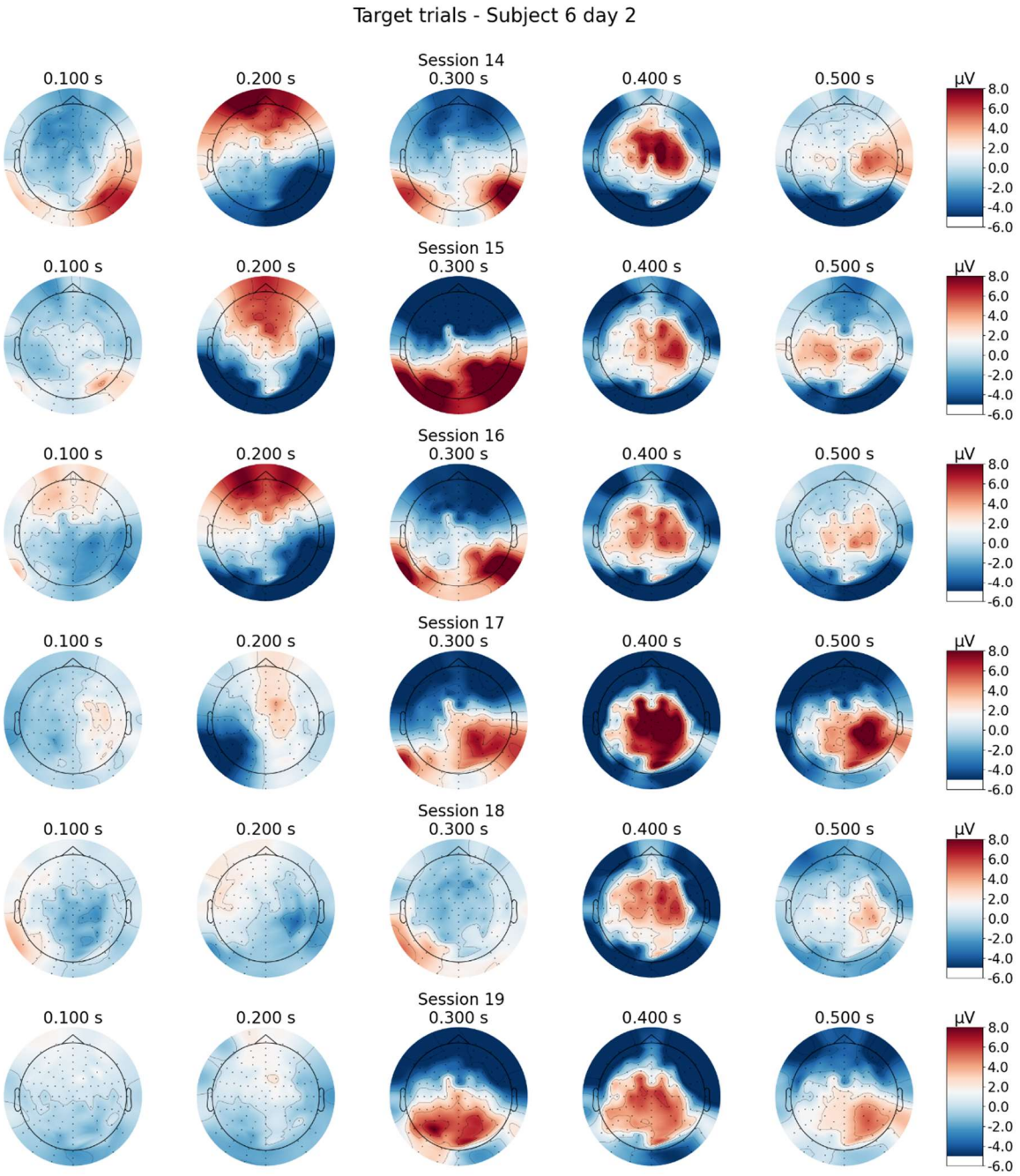


Figure 107: Topographic maps of event related potentials of Subject 6 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

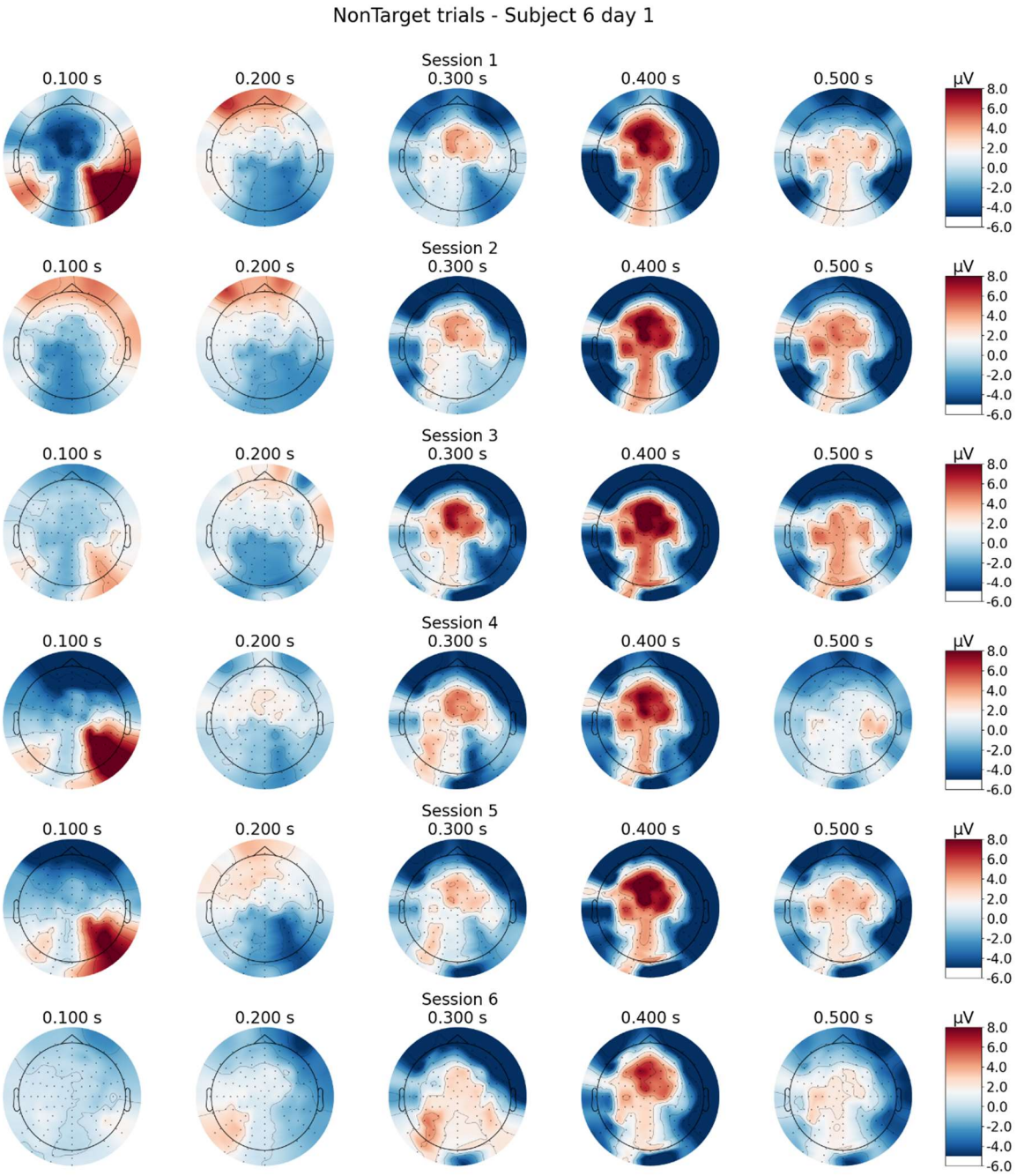


Figure 108: Topographic maps of event related potentials of Subject 6 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

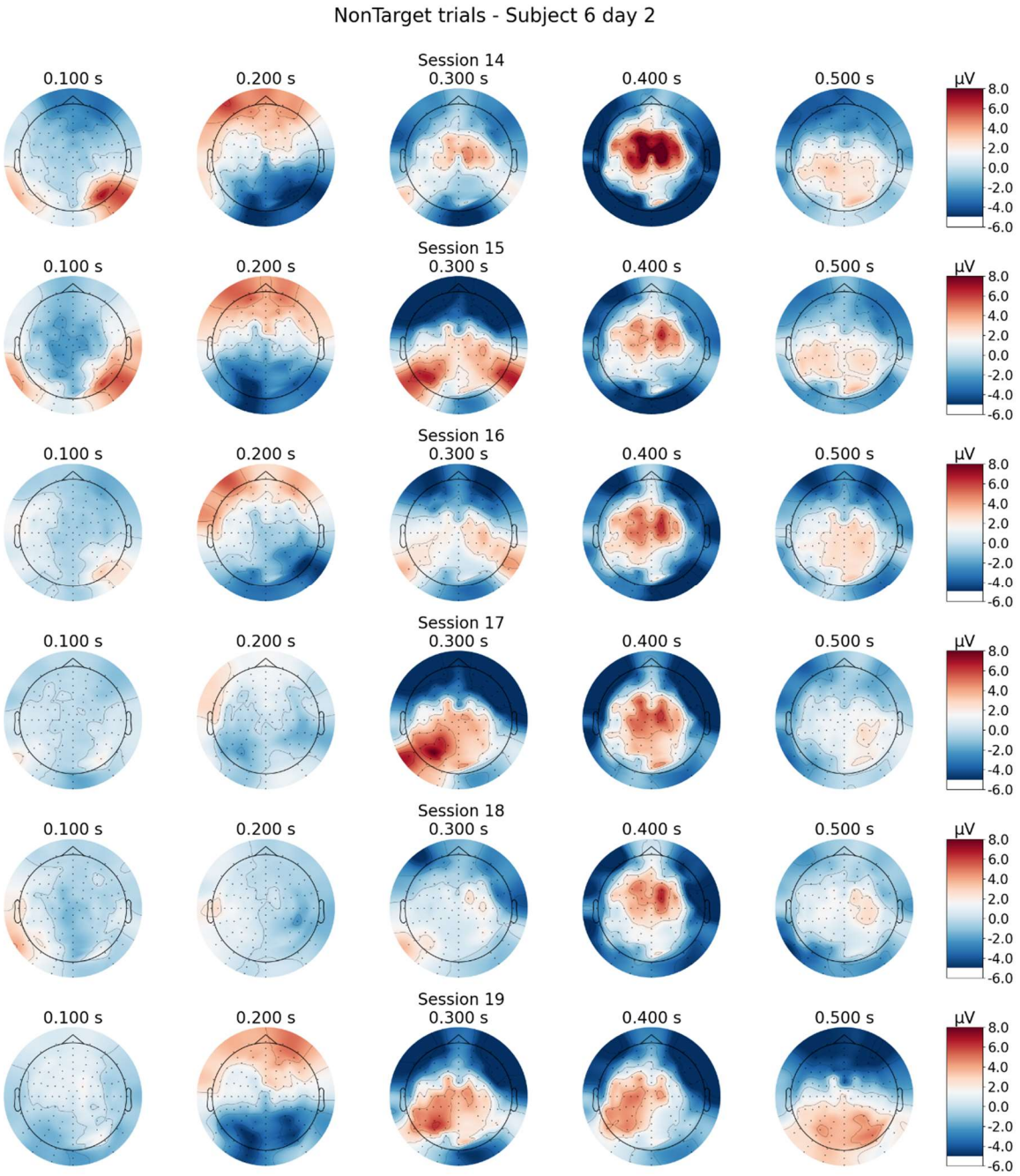


Figure 109: Topographic maps of event related potentials of Subject 6 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.8 Grand average across all subjects

Behavioural data from all participants are presented on Figure 110. Their mean RT was 323.0 ms (SD=34.5 ms), mean accuracy to target trials was 99.8% (SD=0.2%), and mean accuracy to Non-Target trial was 98.8% (SD=0.7%).

5.3.8.1 Behavioural analyses

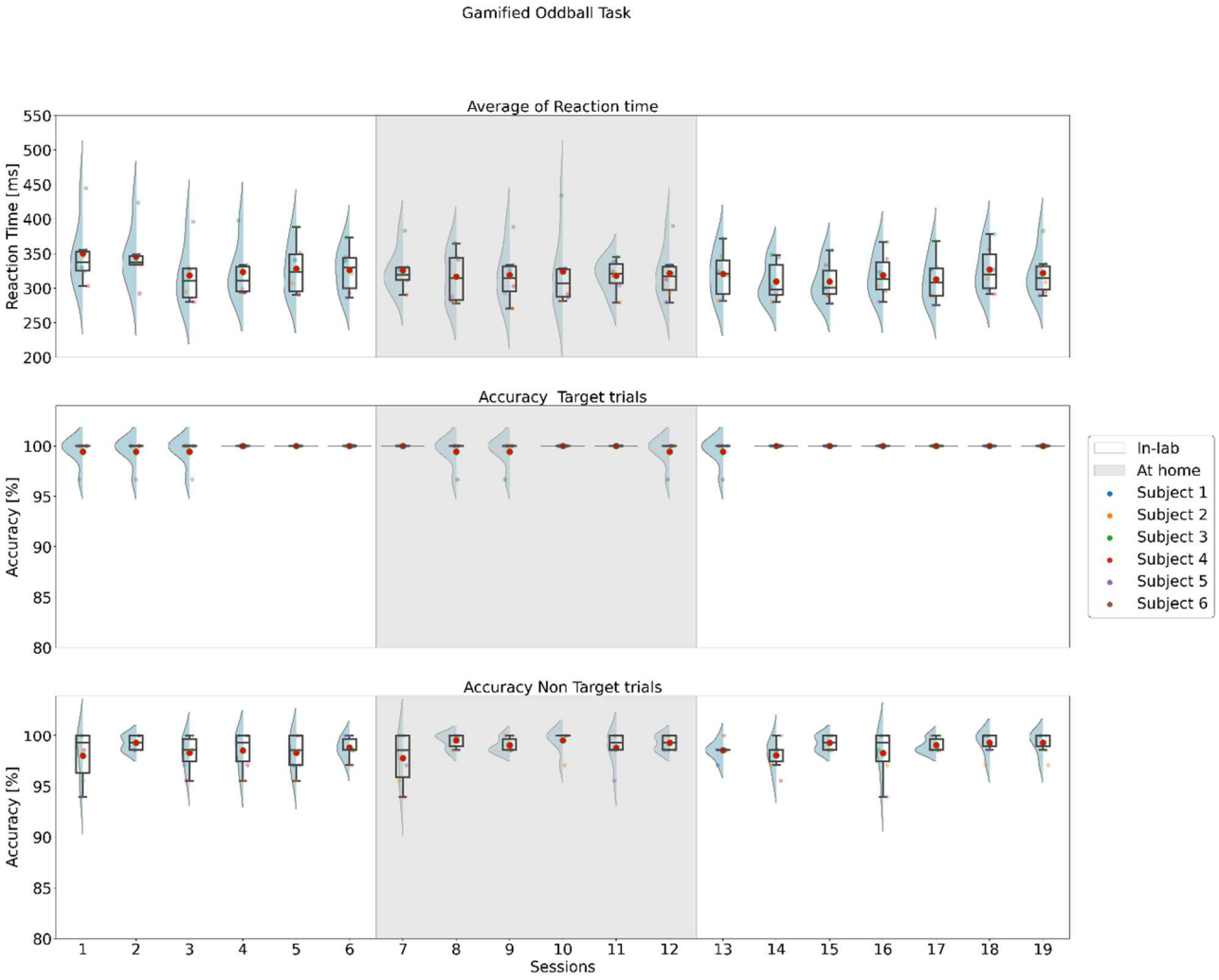


Figure 110: Behavioural responses of all subjects. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.8.2 EEG analyses

Grand average EEG data from all participants are presented on Figures 111 to 117. The typical positive deflection of the P300 is again observed around 300ms post stimulus presentation; just after early sensory perceptual components happening between 0 to 250ms. The Non-Target P300 amplitude is peaking at electrode FCz and decreases the further posterior we look over the scalp. On the other hand, the Target P300 seems to be maximal around the centro-parietal regions, that is at electrode CPz. When examining the ERP image (Figure 111), it seems that Non-Target amplitude may be decreasing across days and sessions.

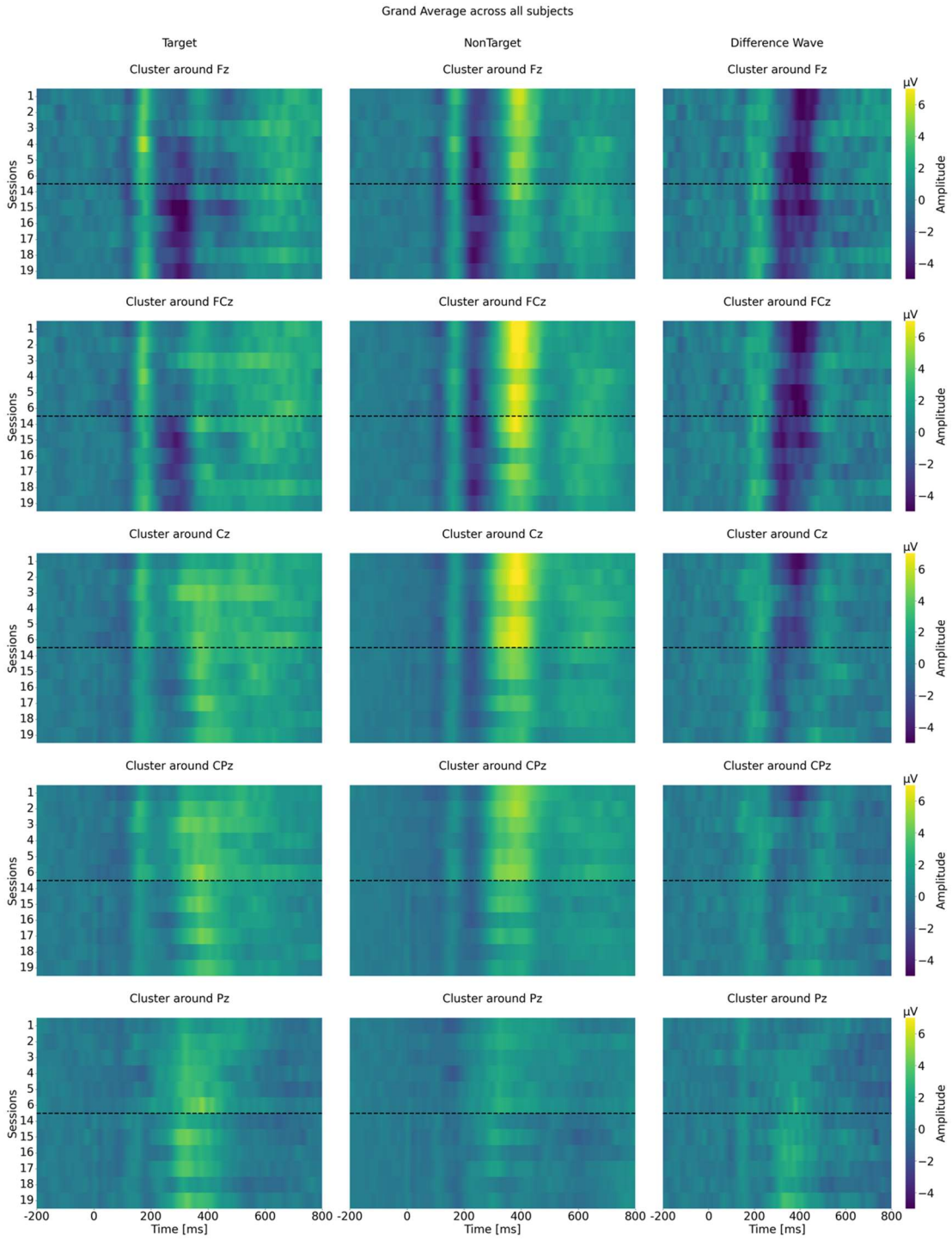


Figure 111: Mean event-related potentials for each session extracted around clusters of interest for all subjects. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

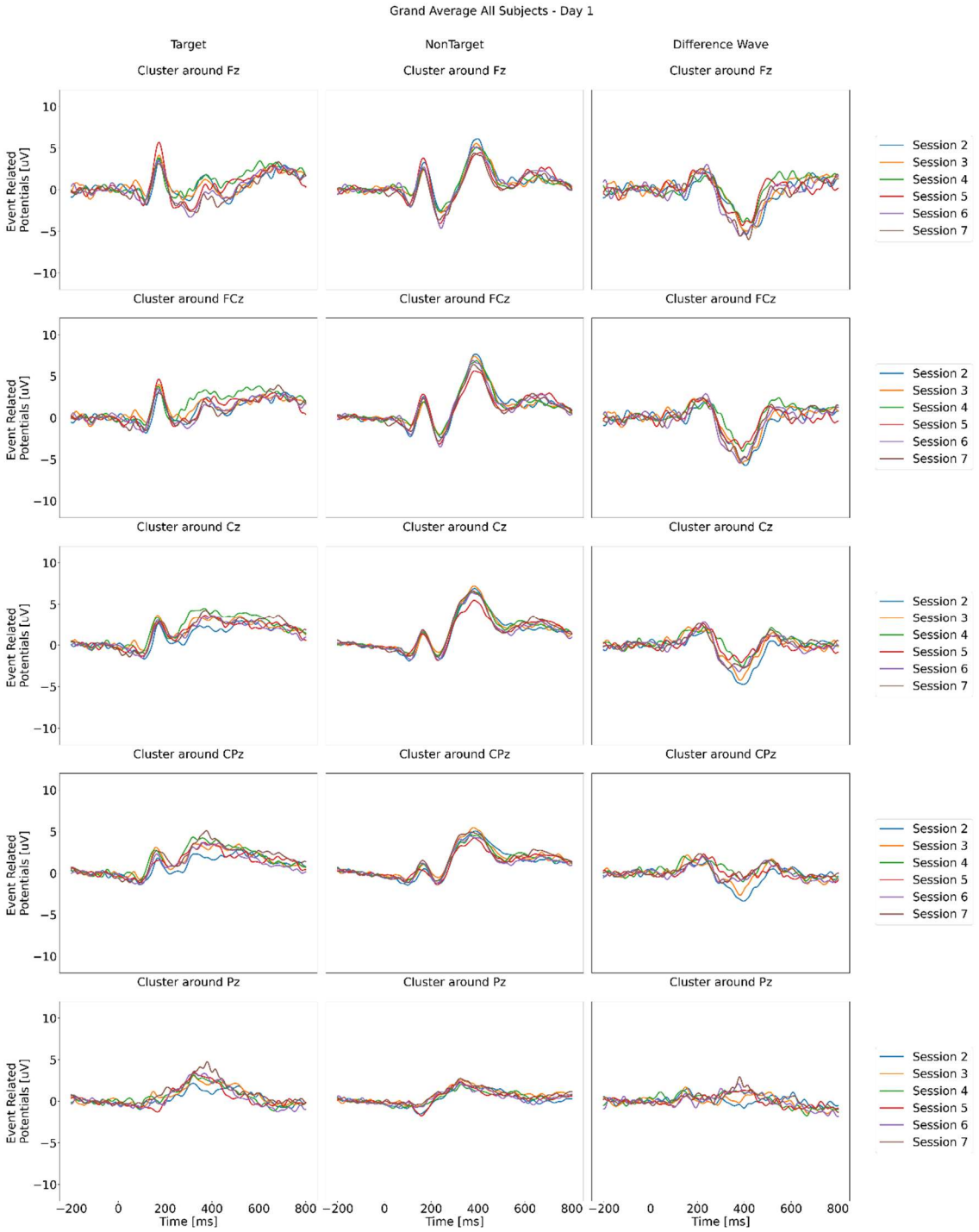


Figure 112: Event Related potentials traces around clusters of electrodes of interest for all subjects during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

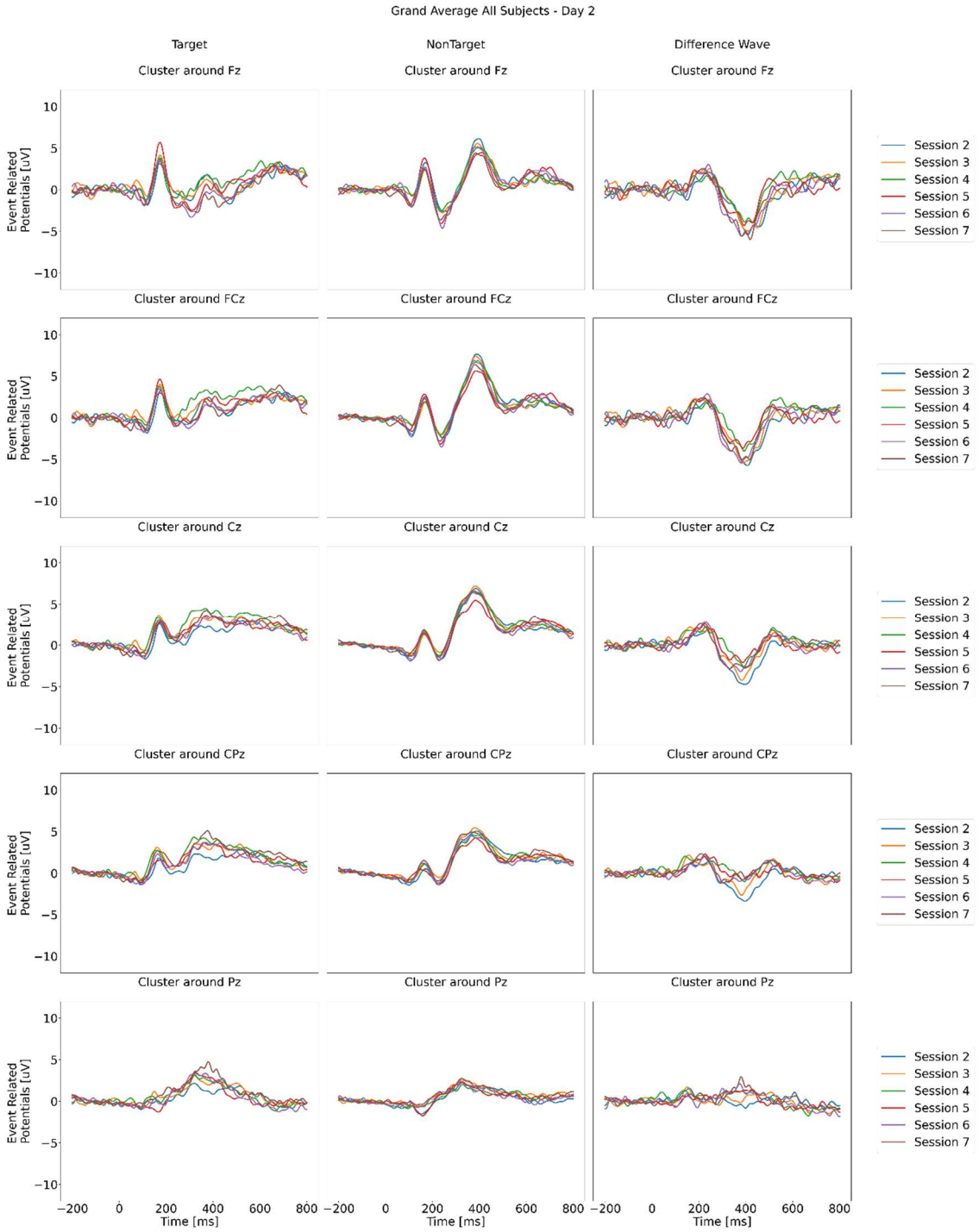


Figure 113: Event Related potentials traces around clusters of electrodes of interest for all subjects during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

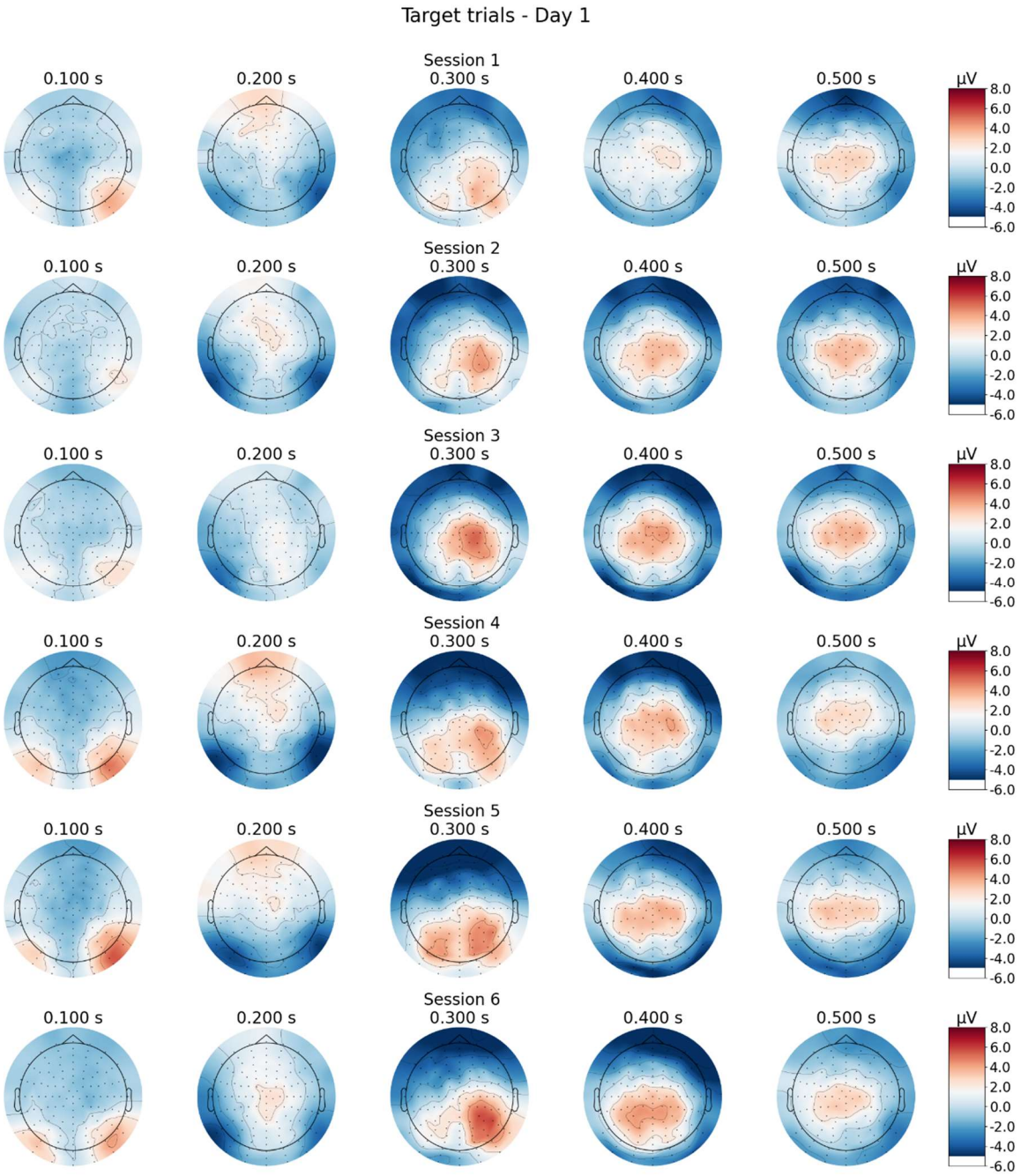


Figure 114: Topographic maps of event related potentials of all subjects to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

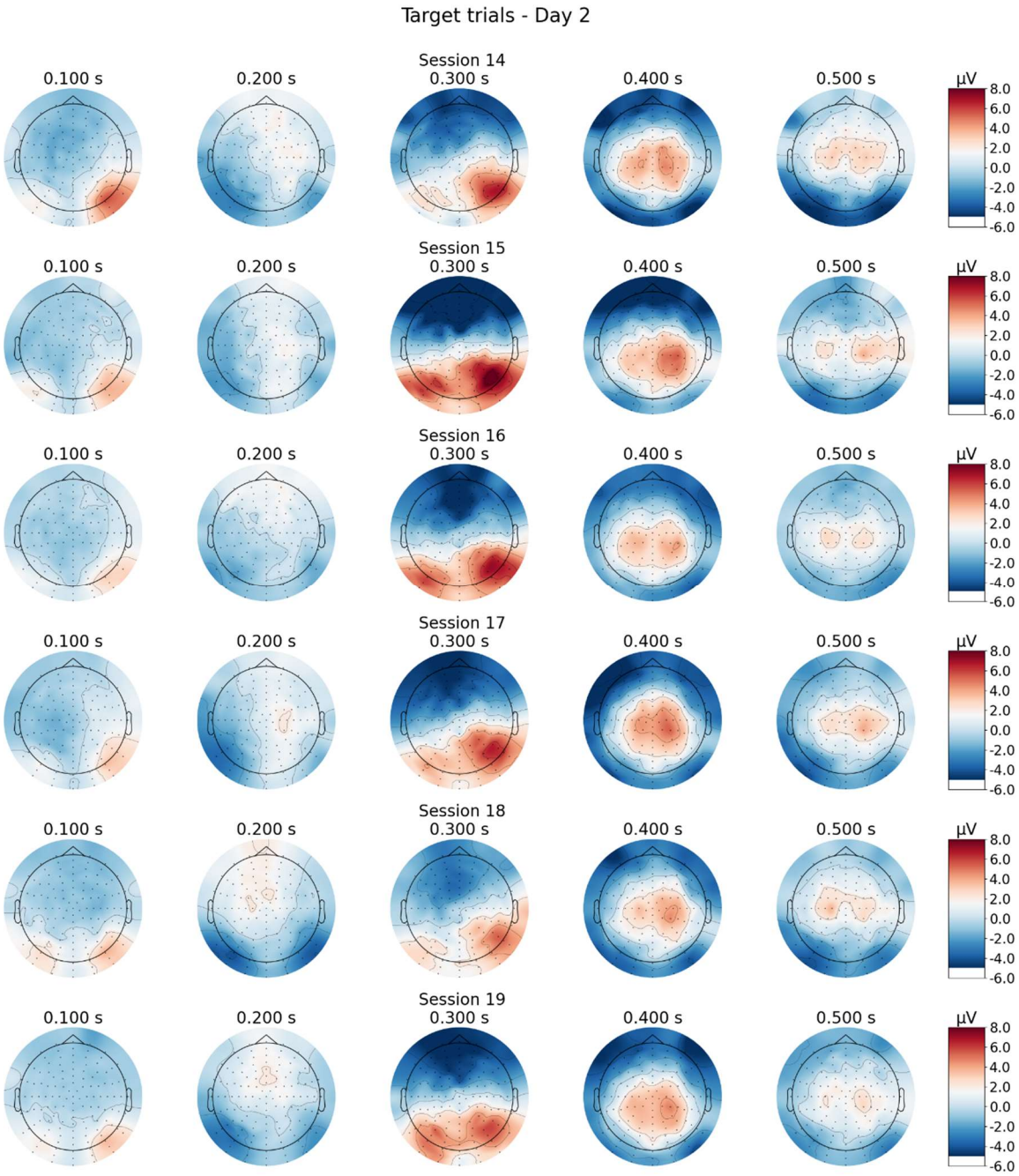


Figure 115: Topographic maps of event related potentials of all subjects to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

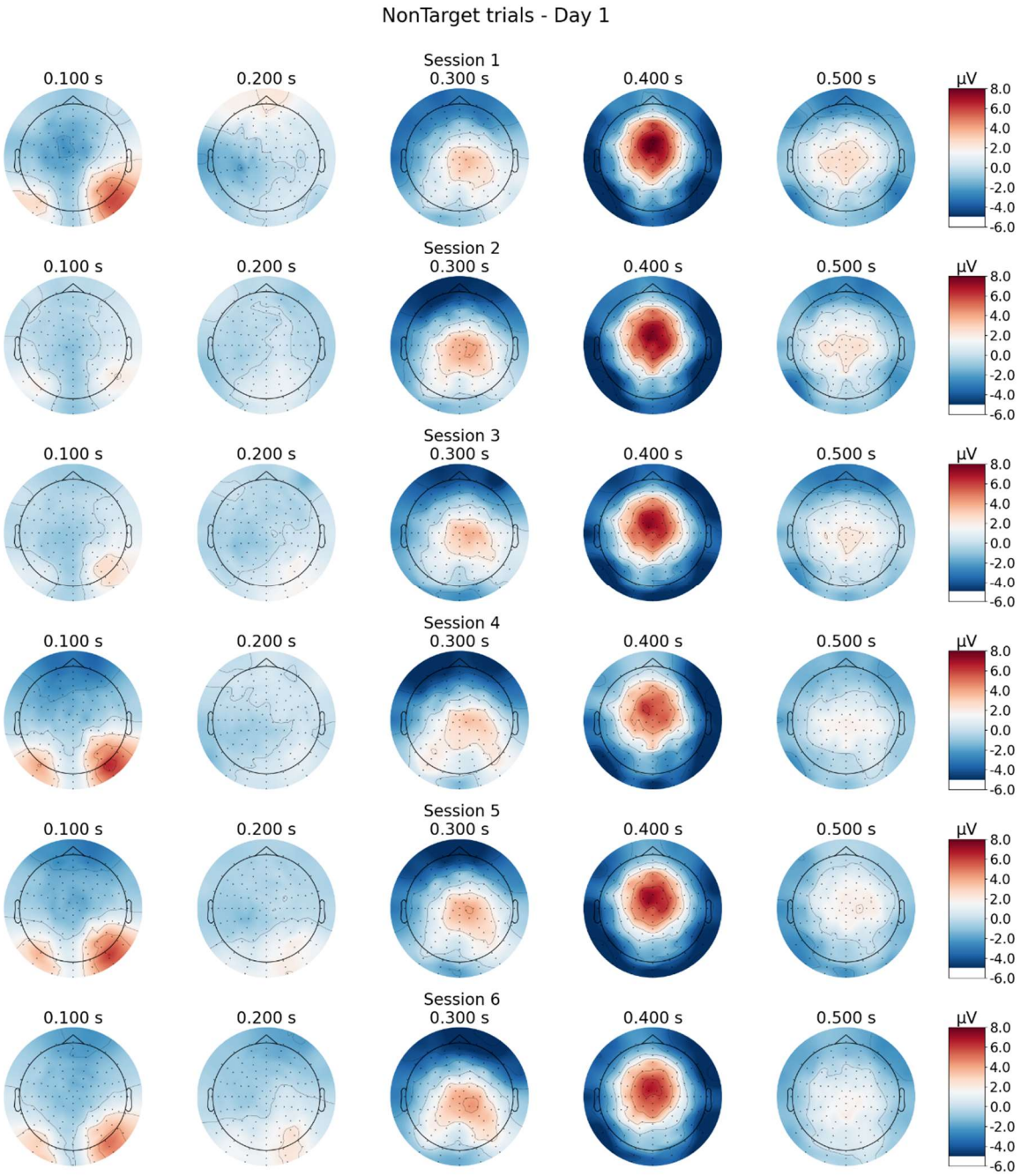


Figure 116: Topographic maps of event related potentials of all subjects to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

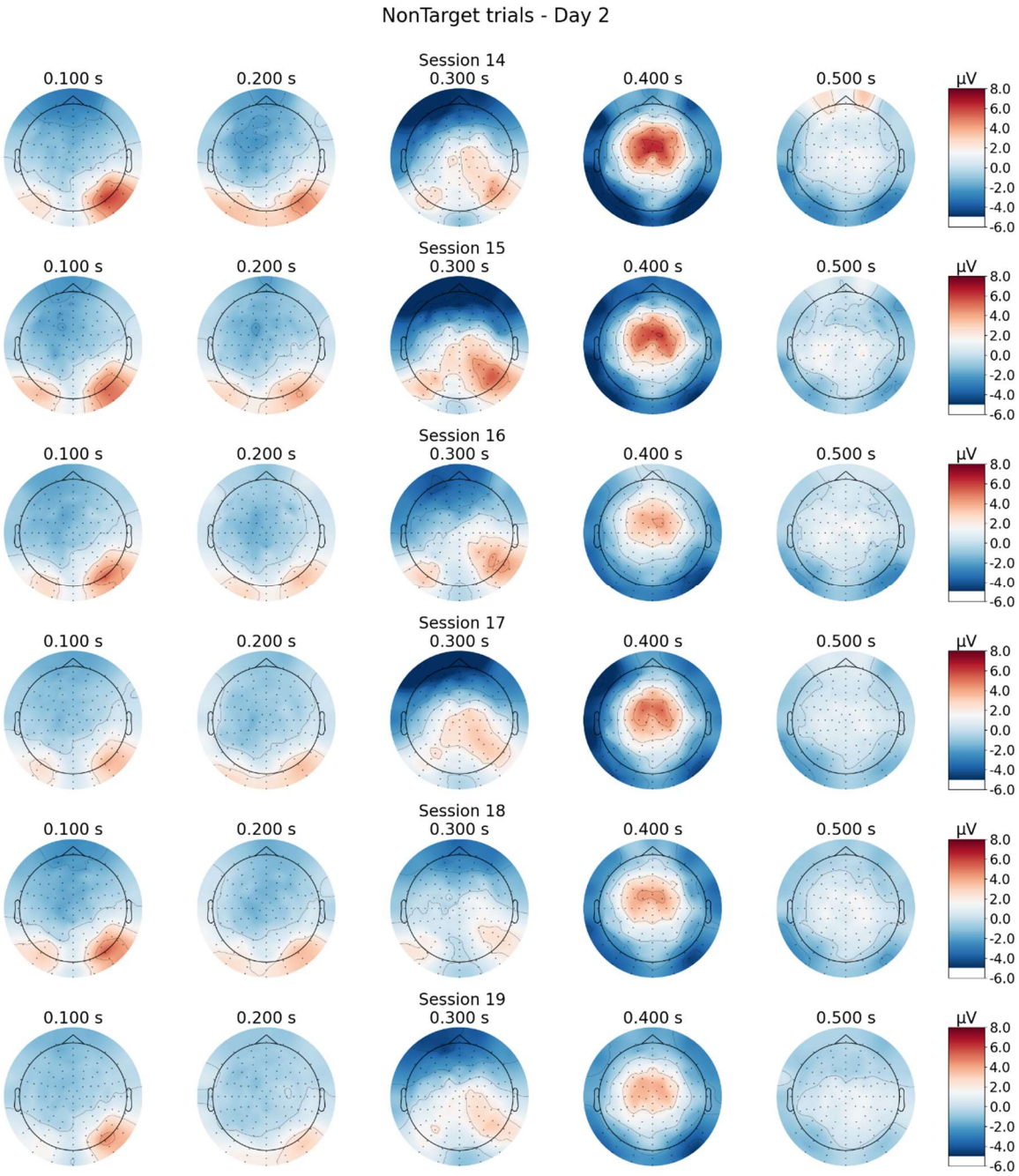


Figure 117: Topographic maps of event related potentials of all subjects to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.9 Excluded participants

5.3.9.1 Subject 7

Subject 7 was a 25-year-old right-handed male. Their questionnaire revealed that their game strategy changed during the course of the study. They reported focusing on avoiding Non-Target stimuli rather than responding to Target stimuli. They reported prioritizing speed over accuracy. Their mean RT was 323.5ms (SD=25.6ms), mean accuracy to target trials was 99.8% (SD=0.8%), and mean accuracy to Non-Target trial was 98.4% (SD=1.7%). Subject 7 missed one at-home session so only 6 at-home behavioural sessions are presented on Figure 118.

5.3.9.1.1 Questionnaire

	Subject
Which option best describes your strategy at the beginning of the first session	I was trying to avoid astronauts rather than shooting aliens
Which option best describes your strategy by the end of the last session	I was trying to avoid astronauts rather than shooting aliens
Can you remember if your strategy changed at some point during the study?	yes
If so, would you be able to say when?	After the first round
Did any of the game features (such as points or bonus stars) impact your game strategy?	The bonus star was prioritised as it was worth the most points
Did you prioritize speed over accuracy?	Yes
Did you prioritize accuracy over speed?	No
Did you prioritize speed and accuracy equally?	No

Table 26: Questionnaire data from Subject 7.

5.3.9.1.2 Behavioural analysis

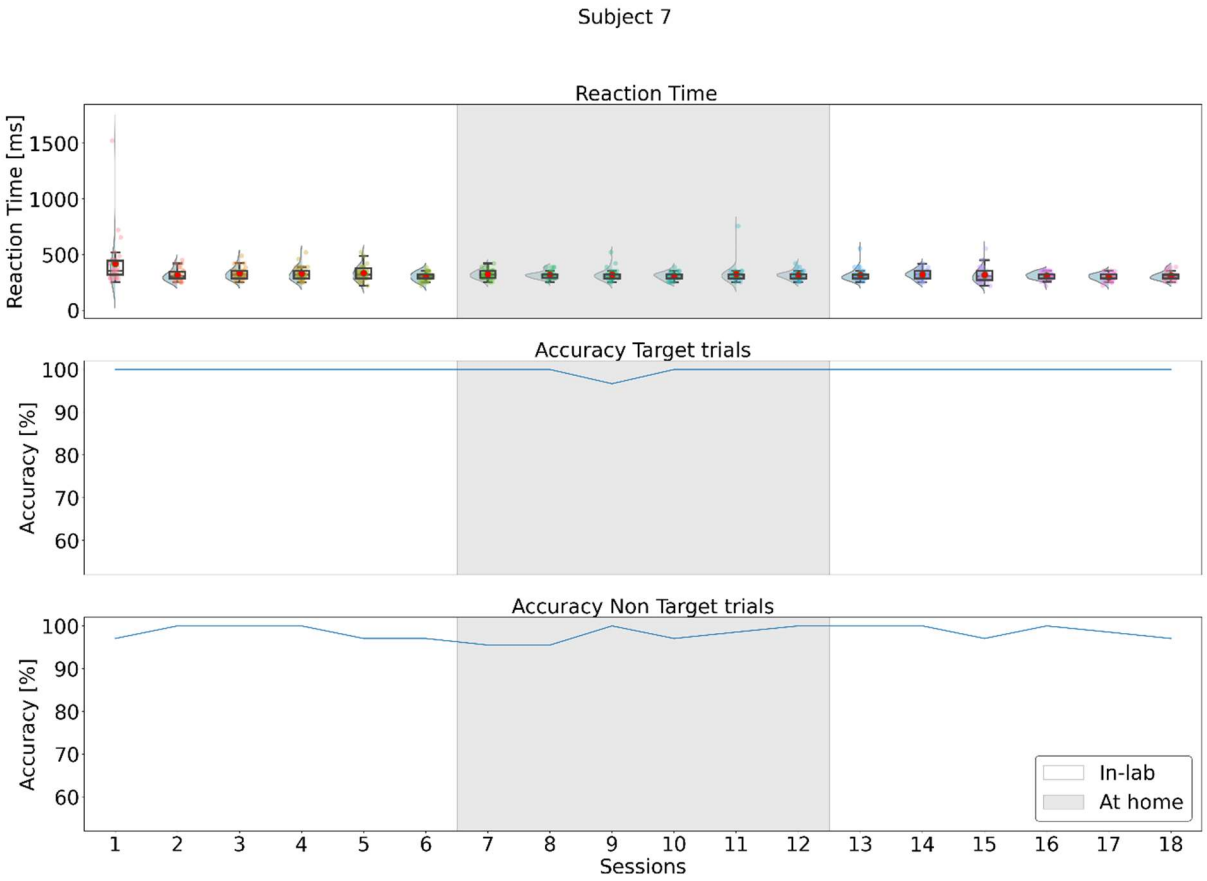


Figure 118: Behavioural responses of Subject 7. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.9.1.3 EEG analysis

EEG data of Subject 7 are presented in Figures 119 to 125. For Non-Target trials, one can observe positive deflections that could correspond to the P300 signal occurring around 300 ms post stimulus presentation. No clear Target P300 signal may be observed. Hints of early sensory perceptual components may be seen between 0 to 250 ms but the amplitudes of the signals are unusually small. The topography of the signals seems to be consistent across conditions with both Target and Non-Target trials peaking around central regions. The amplitudes of the P300 extracted from Target trials are smaller than the ones extracted from Non-Target trials as demonstrated by the negative the difference waves presented in Figures 120 and 121. When examining the ERP image (Figure 119) and the topographic maps (Figures 122 to 125), it is difficult to discern a clear pattern of amplitude modulation across time for both the Target and Non-Target conditions.

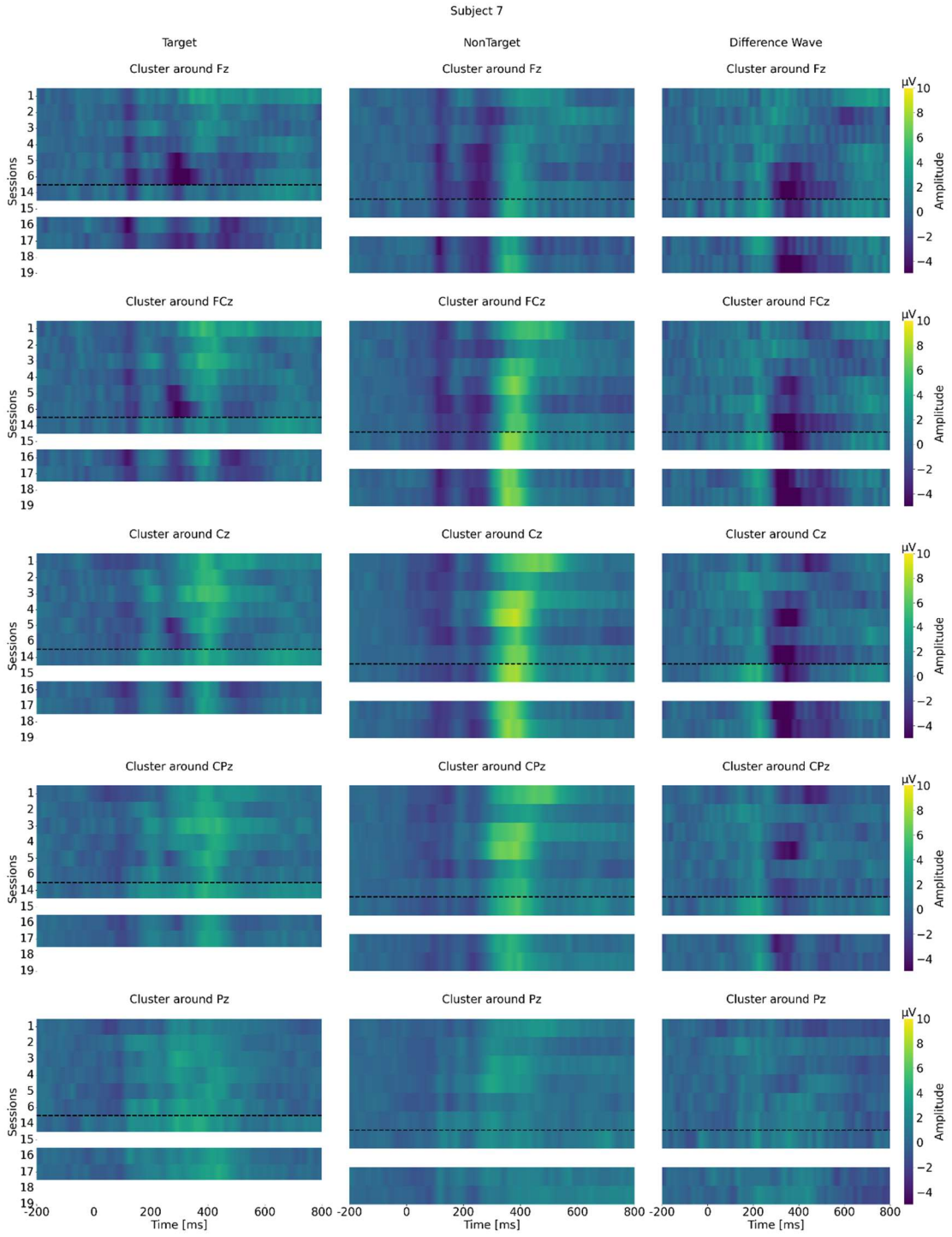


Figure 119: Mean event-related potentials for each session extracted around clusters of interest for Subject 7. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

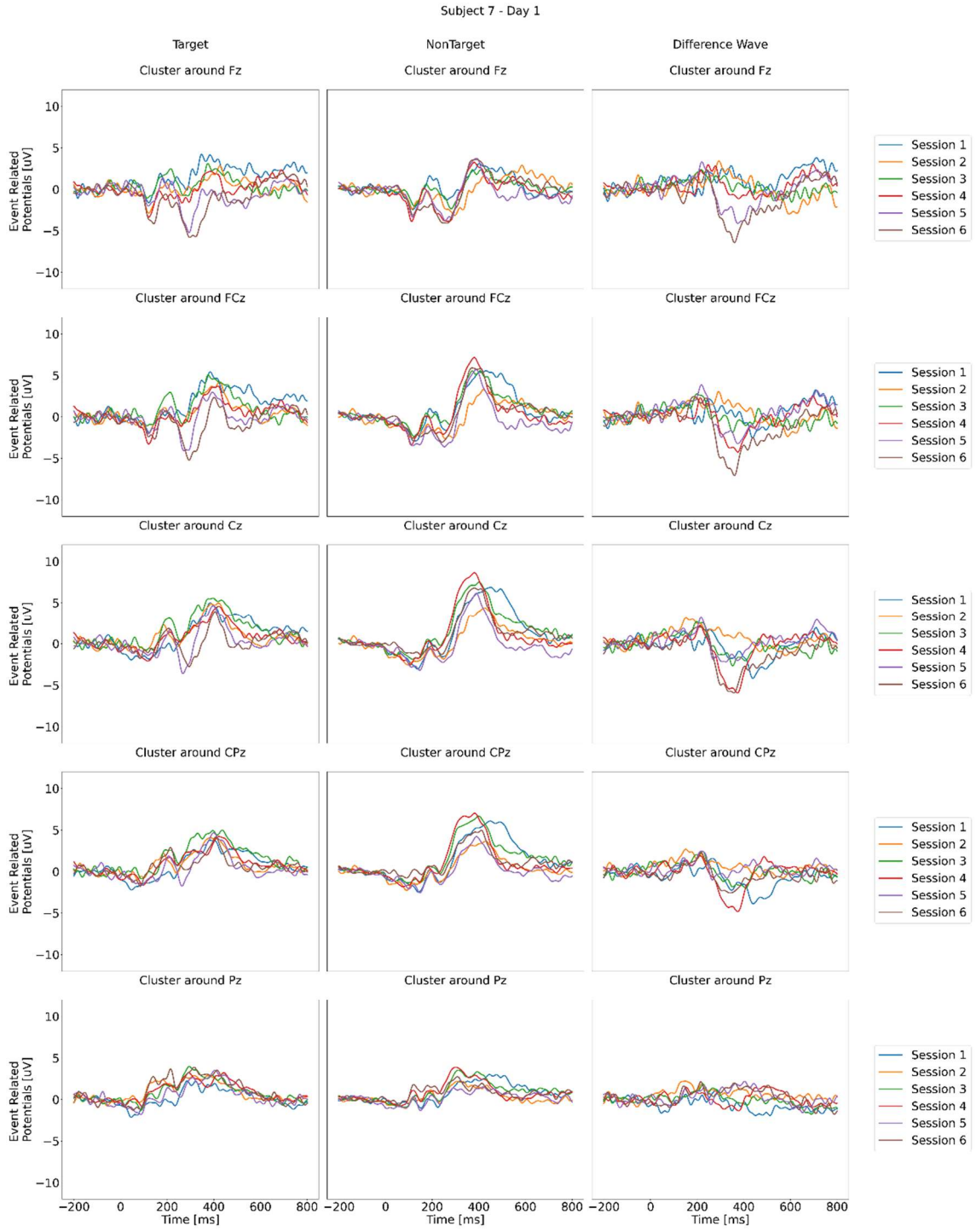


Figure 120: Event Related potentials traces around clusters of electrodes of interest for Subject 7 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

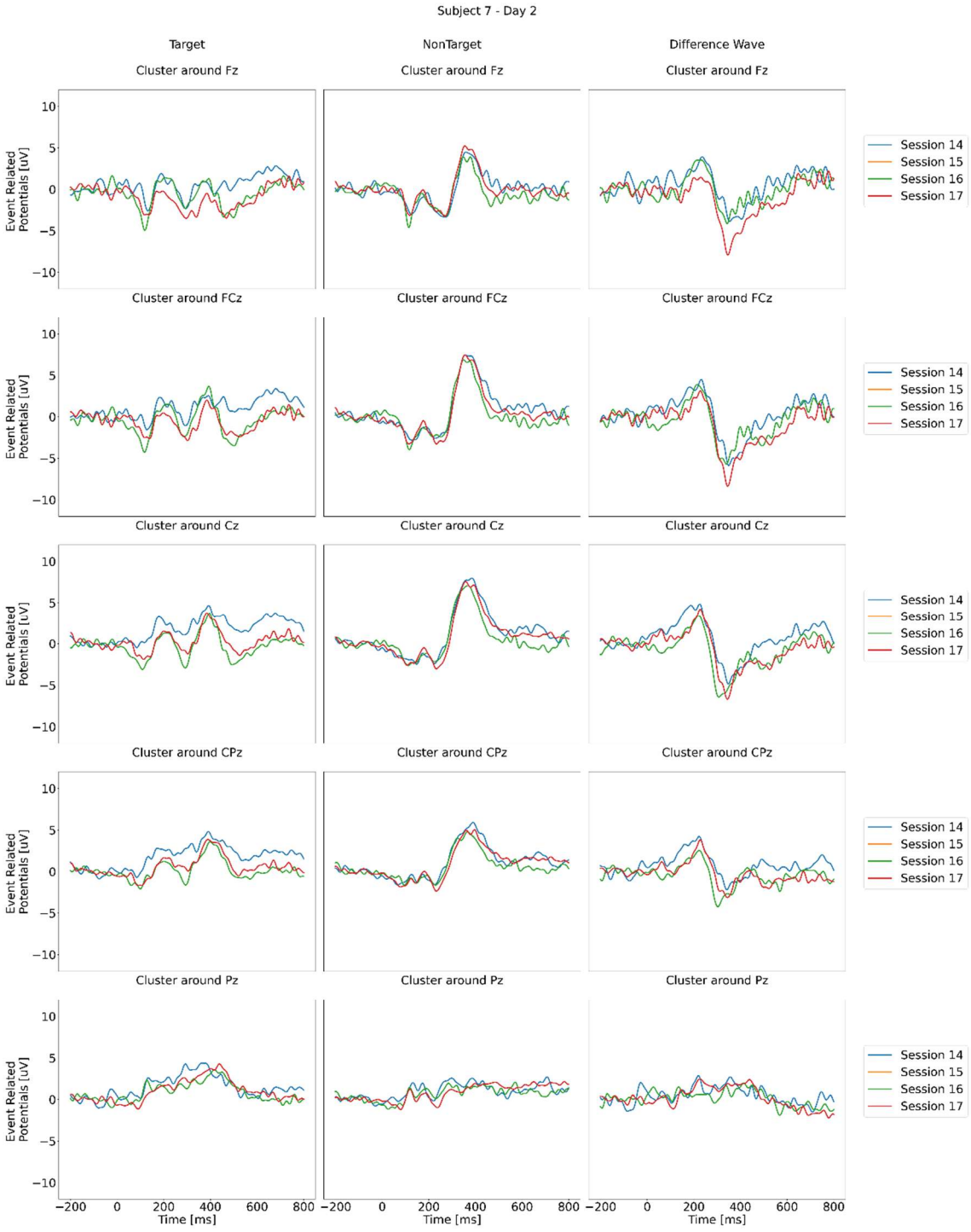


Figure 121: Event Related potentials traces around clusters of electrodes of interest for Subject 7 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

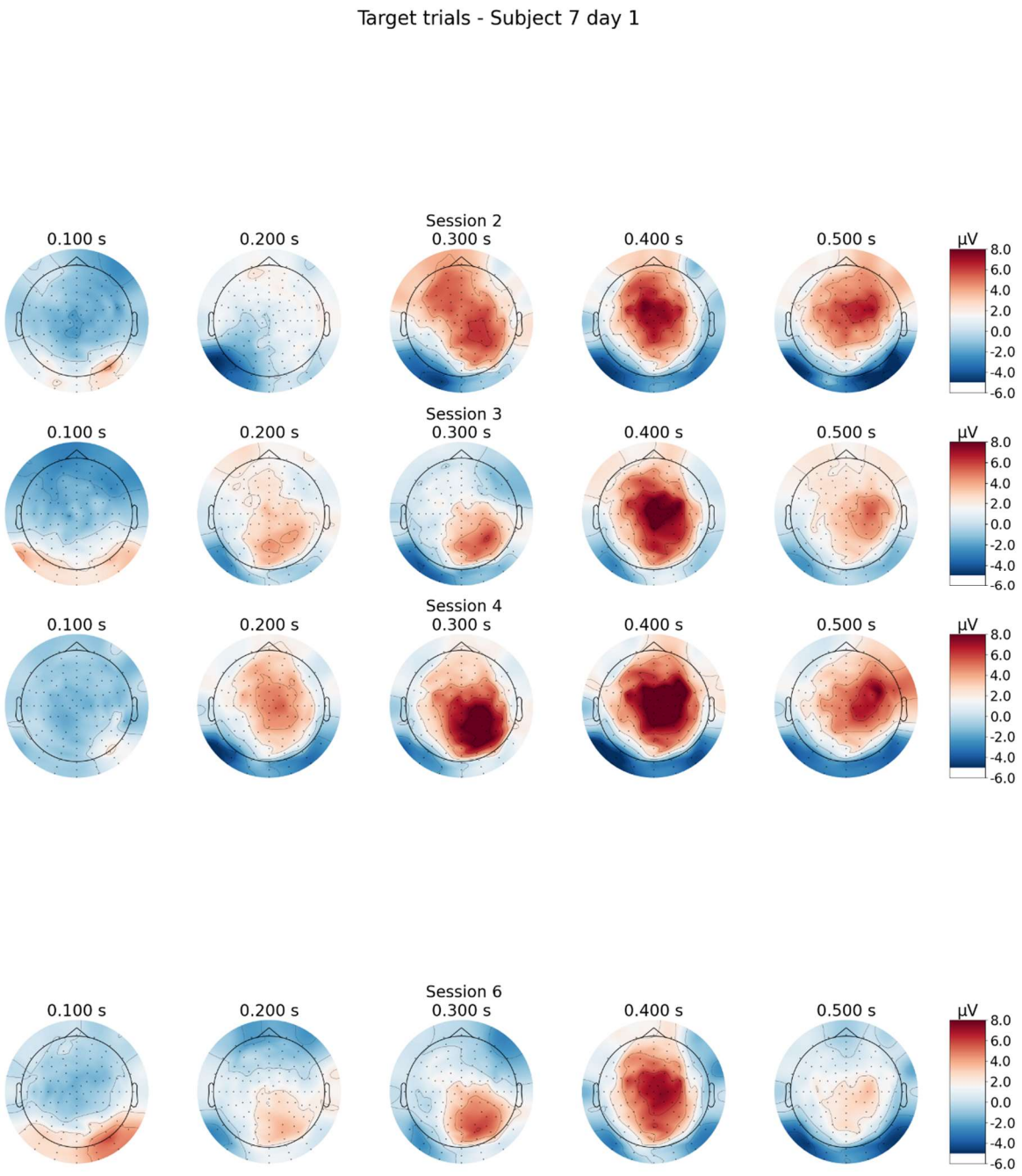


Figure 122: Topographic maps of event related potentials of Subject 7 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

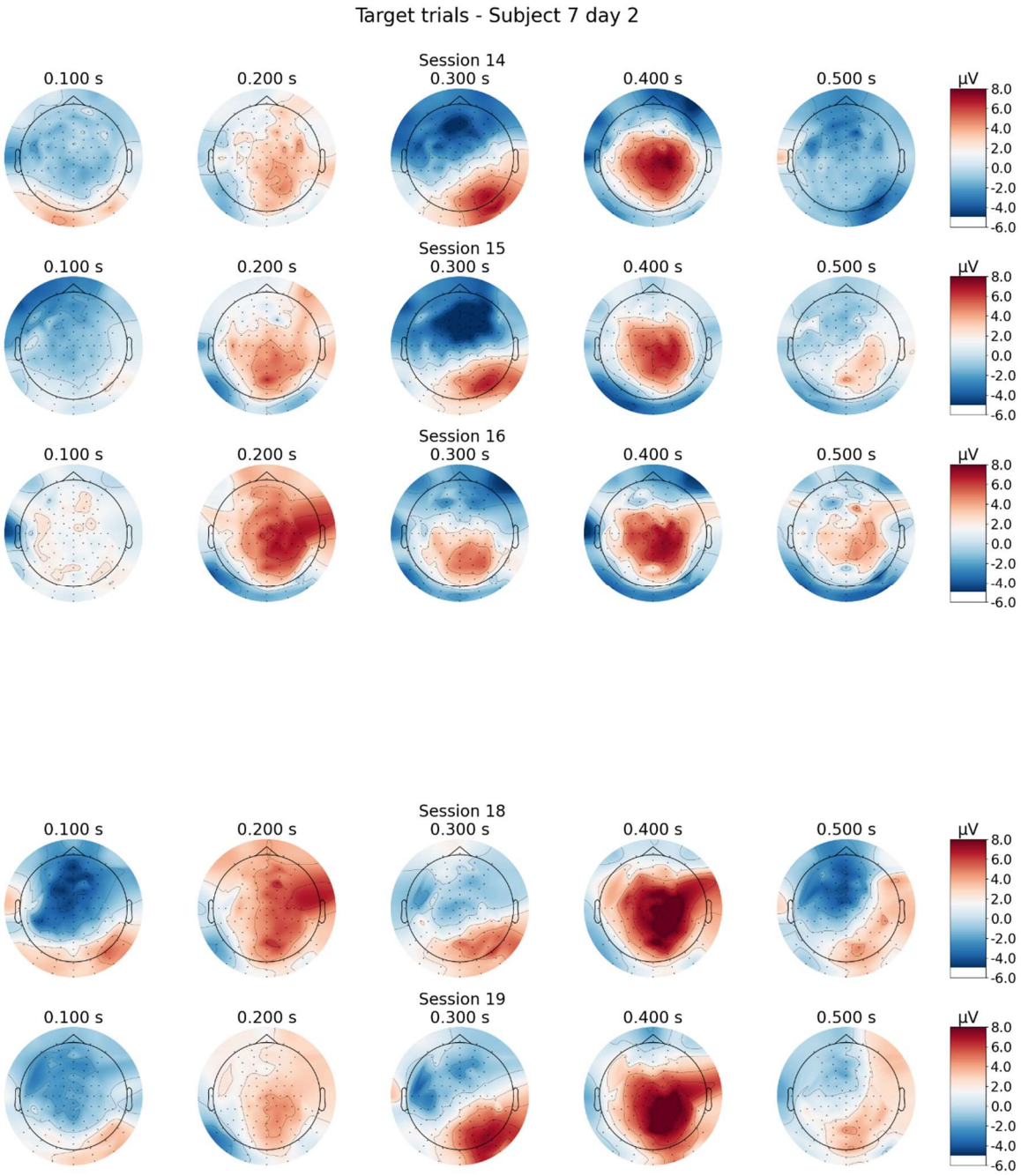


Figure 123: Topographic maps of event related potentials of Subject 7 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

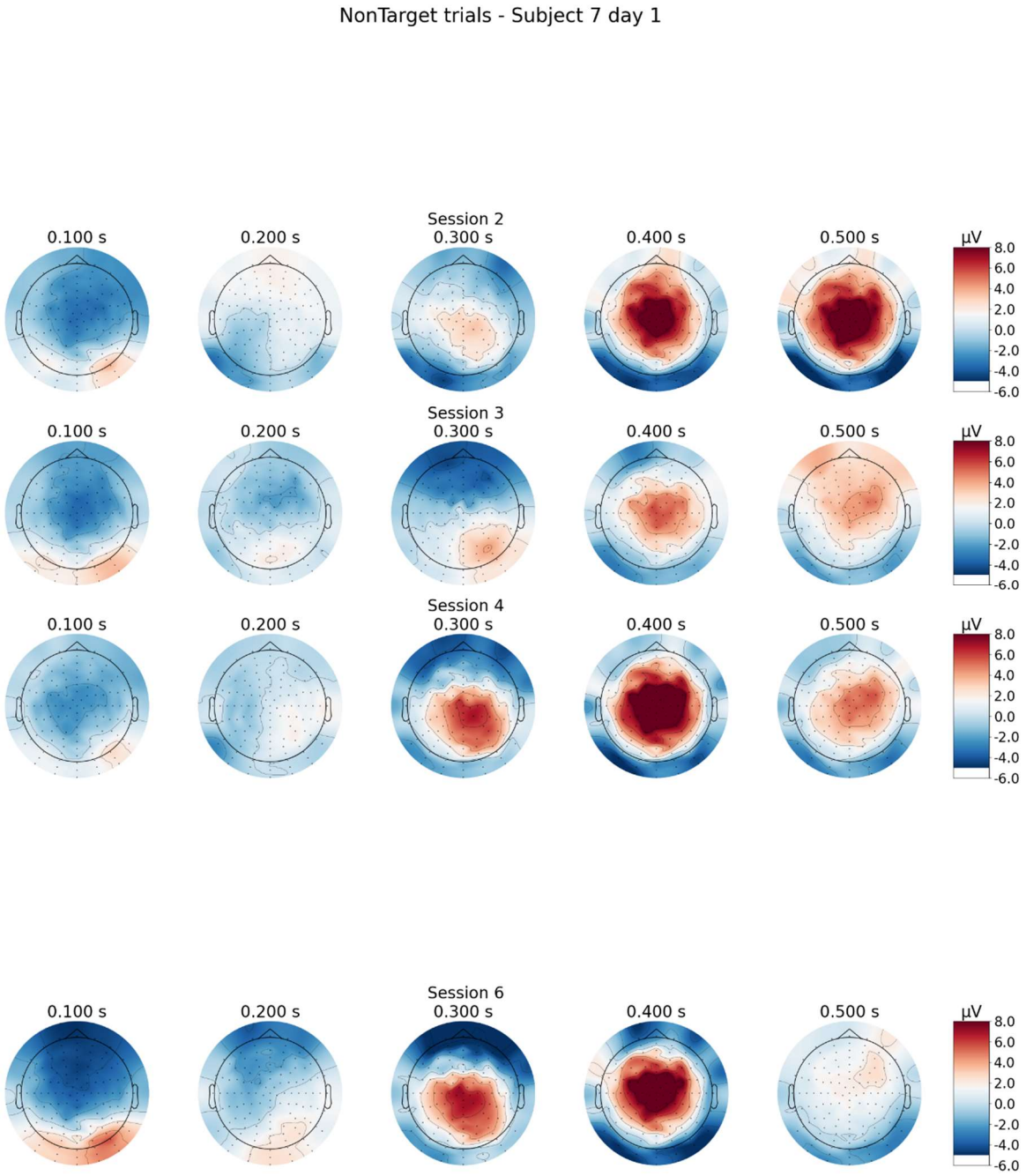


Figure 124: Topographic maps of event related potentials of Subject 7 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

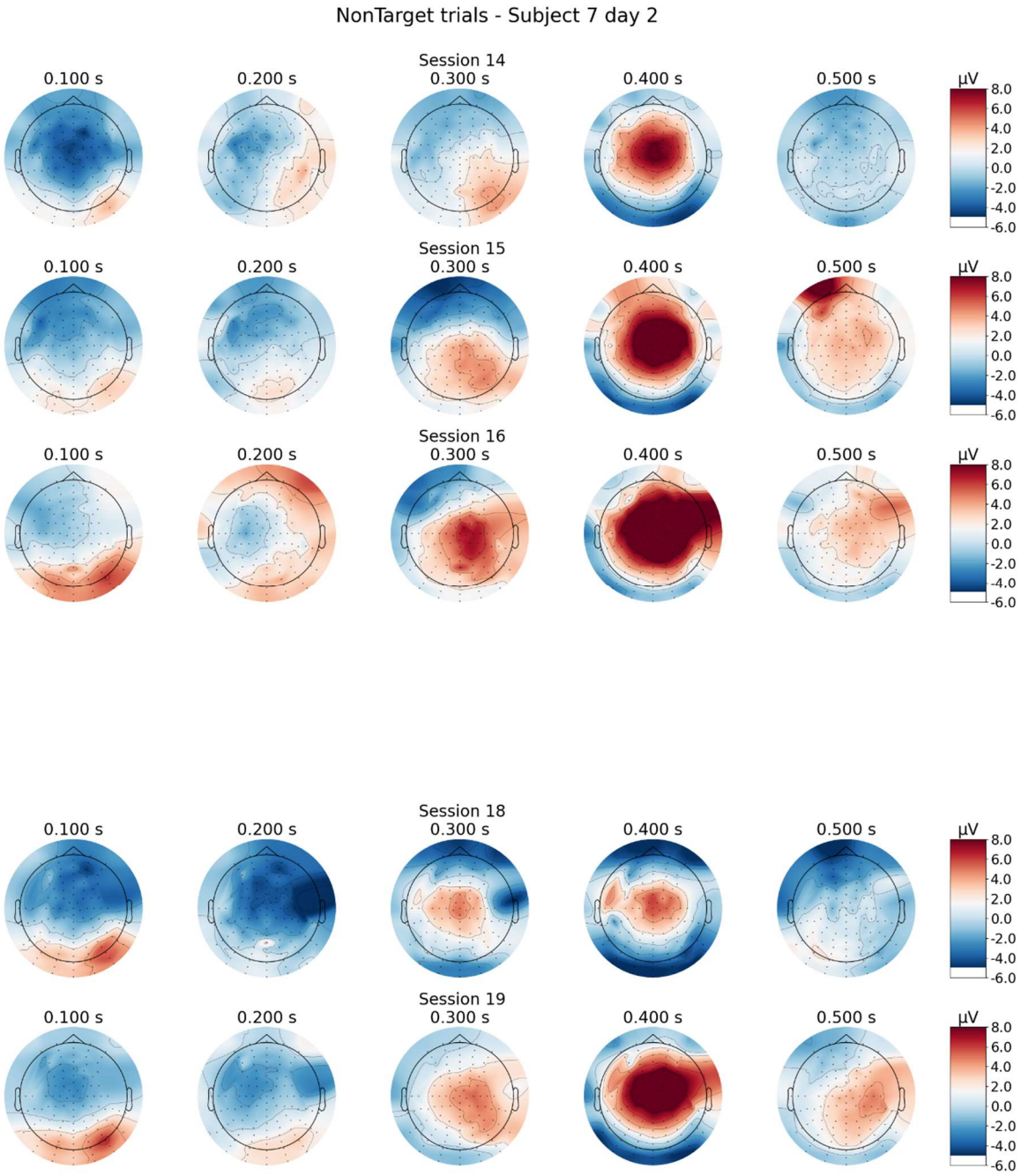


Figure 125: Topographic maps of event related potentials of Subject 7 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.9.2 Subject 8

Subject 8 was a 25-year-old right-handed male. Their questionnaire revealed that their game strategy did not change during the course of the study. They reported focusing on responding to Target stimuli. They reported prioritizing accuracy over speed. Their mean RT was 415.6ms (SD=50.0ms), mean accuracy to target trials was 91.7% (SD=12%), and mean accuracy to Non-Target trial was 95.7% (SD=5.1%). Subject 8 missed one at-home session so only 6 at-home behavioural sessions are presented on Figure 126.

5.3.9.2.1 Questionnaire

	Subject
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	I did not change my strategy
If so, would you be able to say when?	
Did any of the game features (such as points or bonus stars) impact your game strategy?	The number of aliens is much less than astronauts.
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	Yes
Did you prioritize speed and accuracy equally?	No

Table 27: Questionnaire data from Subject 8.

5.3.9.2.2 Behavioural analysis

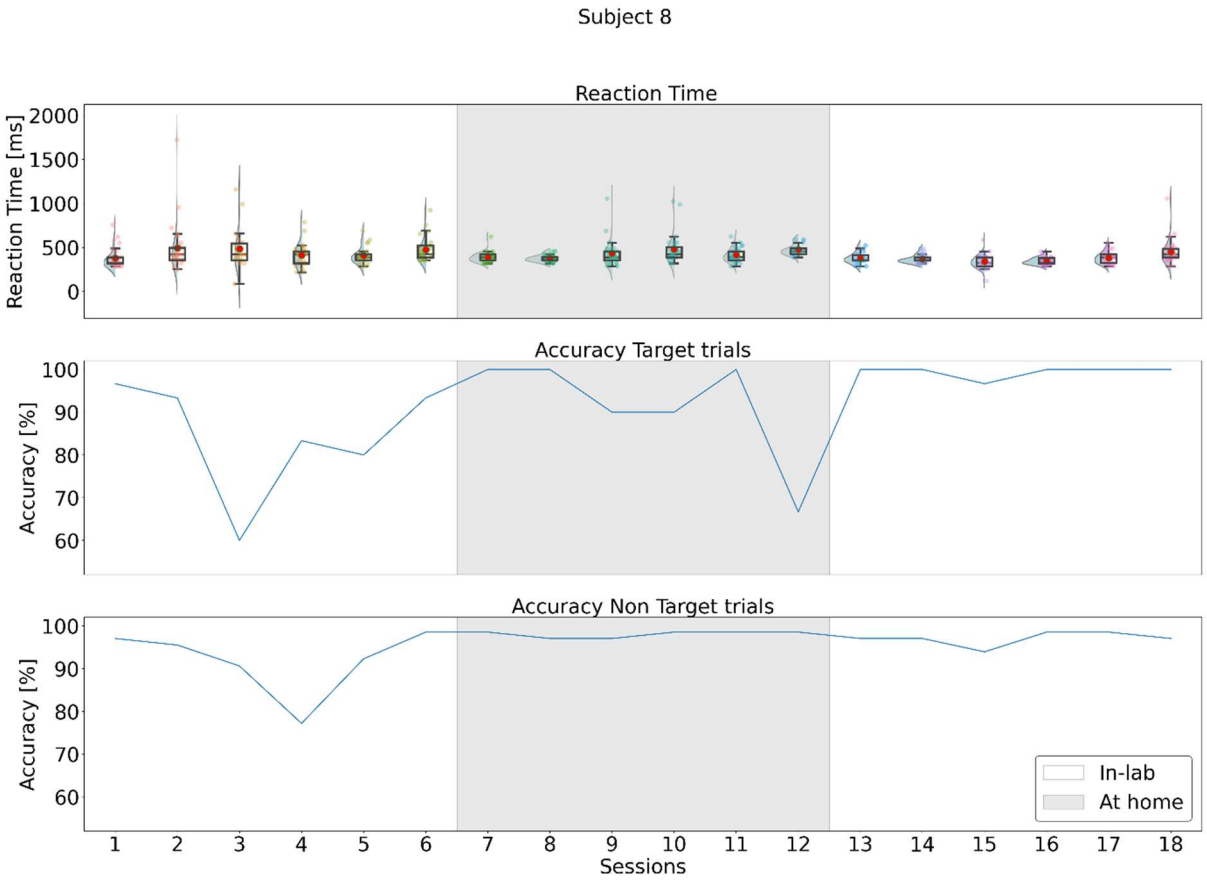


Figure 126: Behavioural responses of Subject 8. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.9.2.3 EEG analysis

EEG data of Subject 8 are presented in Figures 127 to 133. Both for Target and Non-Target trials, hints of early sensory perceptual components can be seen between 0 to 250 ms, although it should be noted that the data is very noisy, and the amplitude of the signals is quite small. It is not possible to distinguish any Target or Non-Target signals.

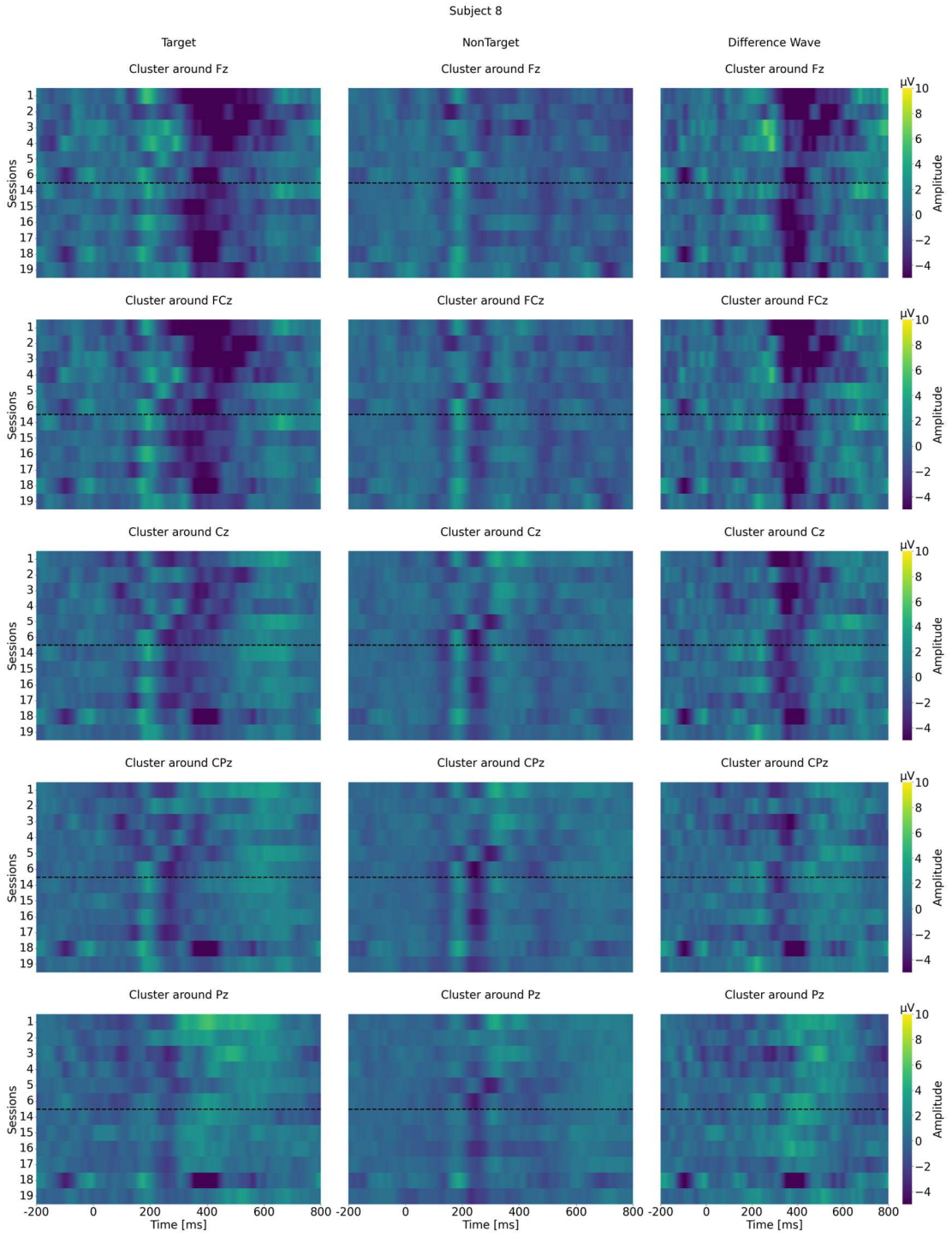


Figure 127: Mean event-related potentials for each session extracted around clusters of interest for Subject 8. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

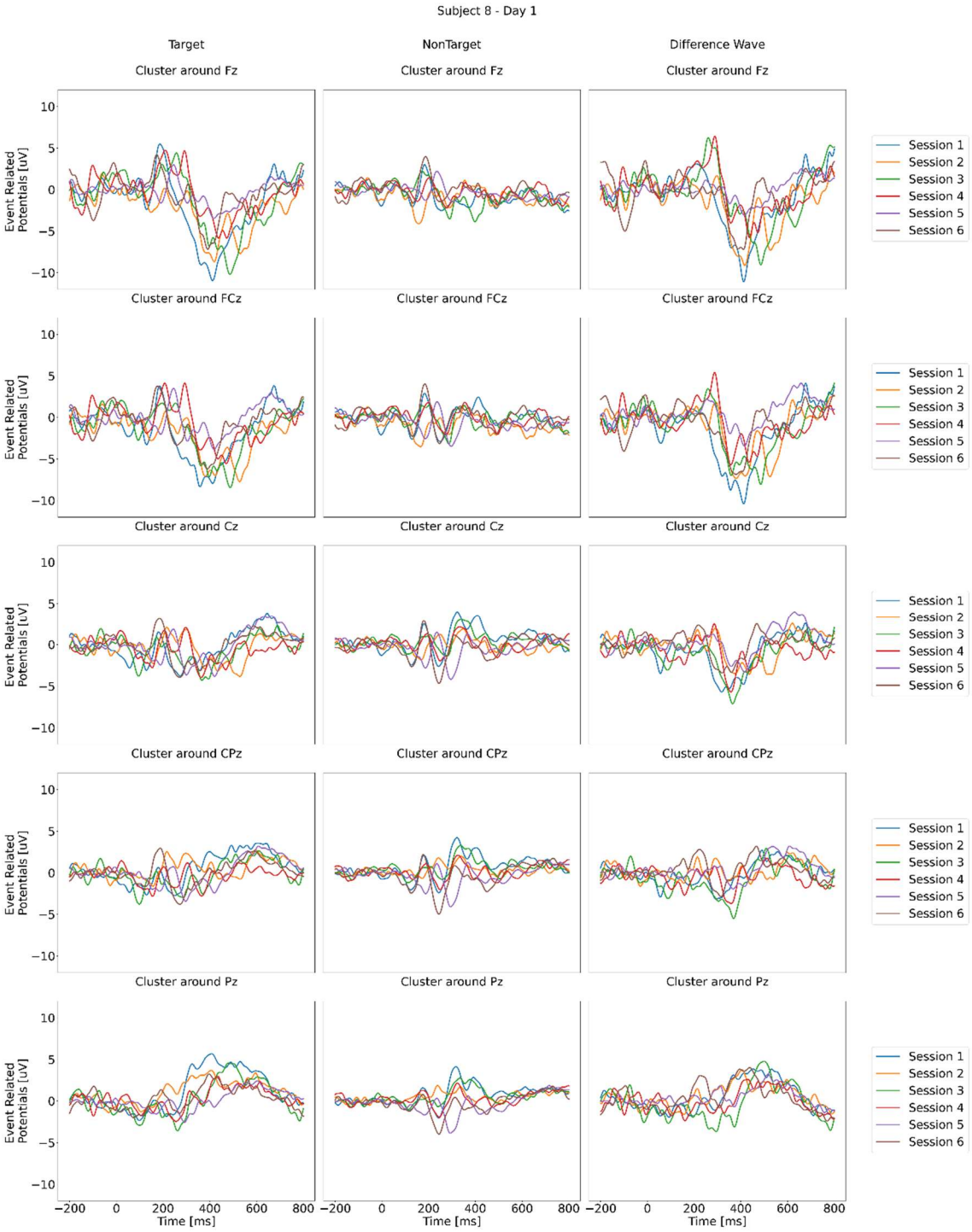


Figure 128: Event Related potentials traces around clusters of electrodes of interest for Subject 8 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

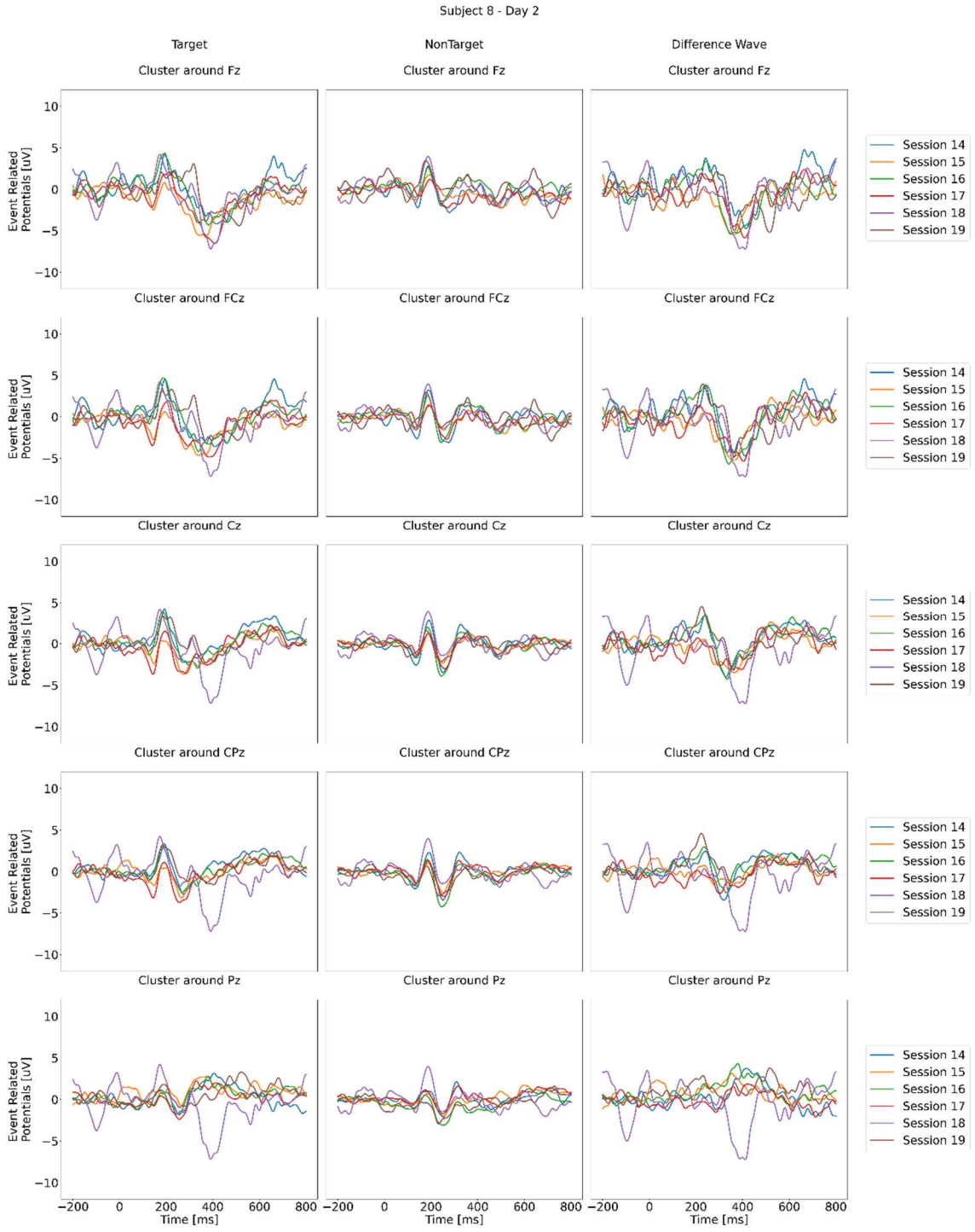


Figure 129: Event Related potentials traces around clusters of electrodes of interest for Subject 8 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

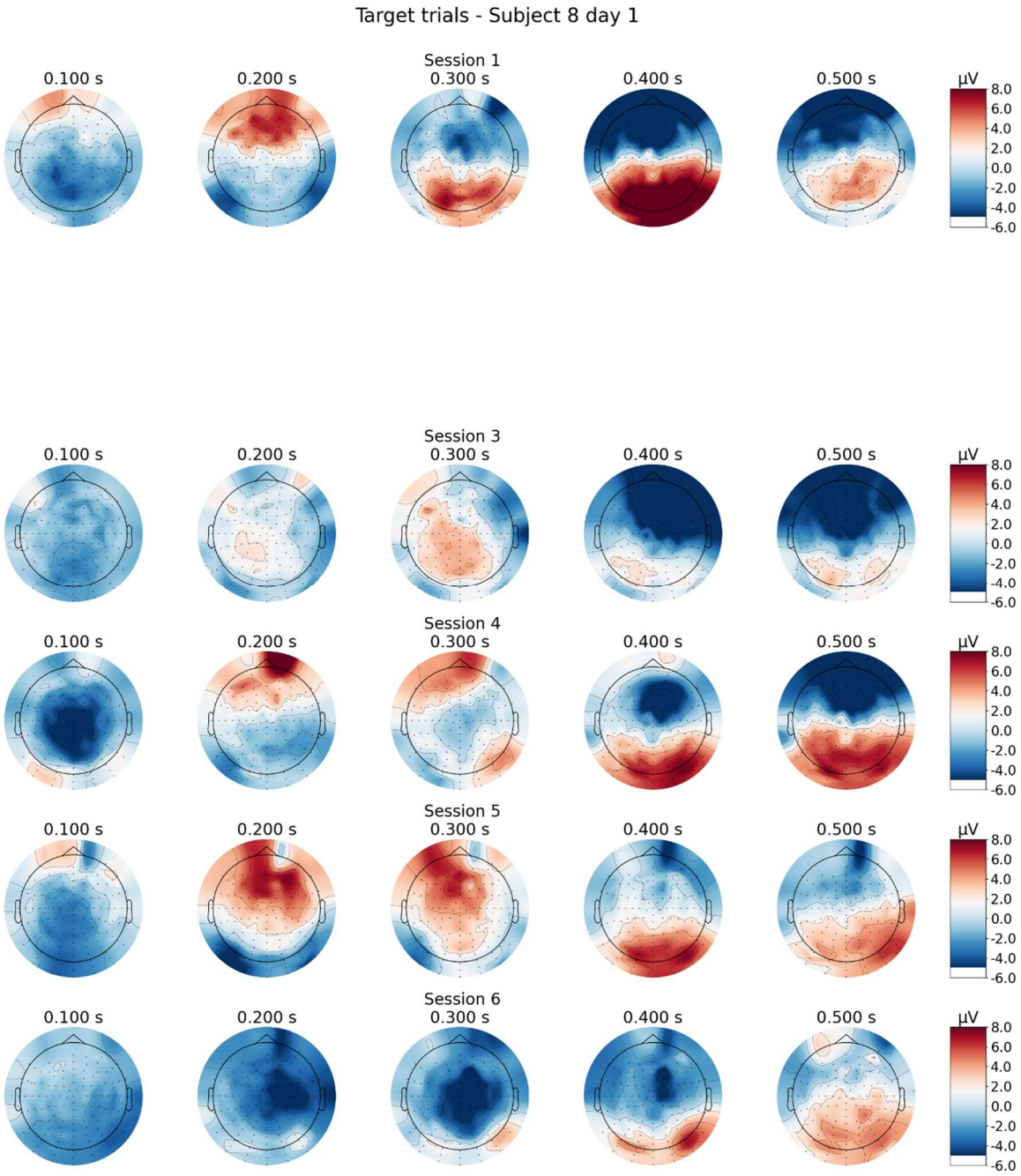


Figure 130: Topographic maps of event related potentials of Subject 8 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

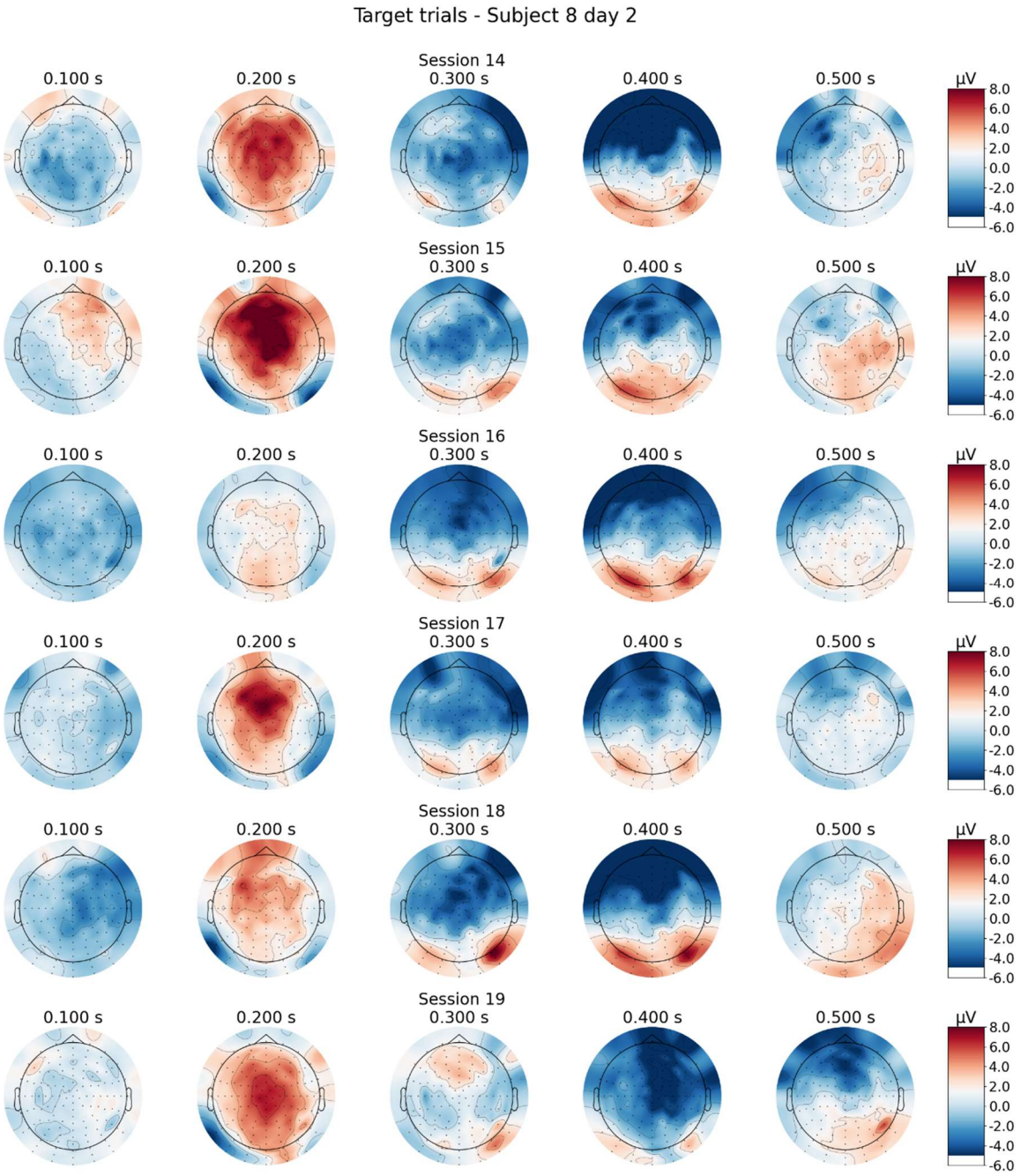


Figure 131: Topographic maps of event related potentials of Subject 8 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

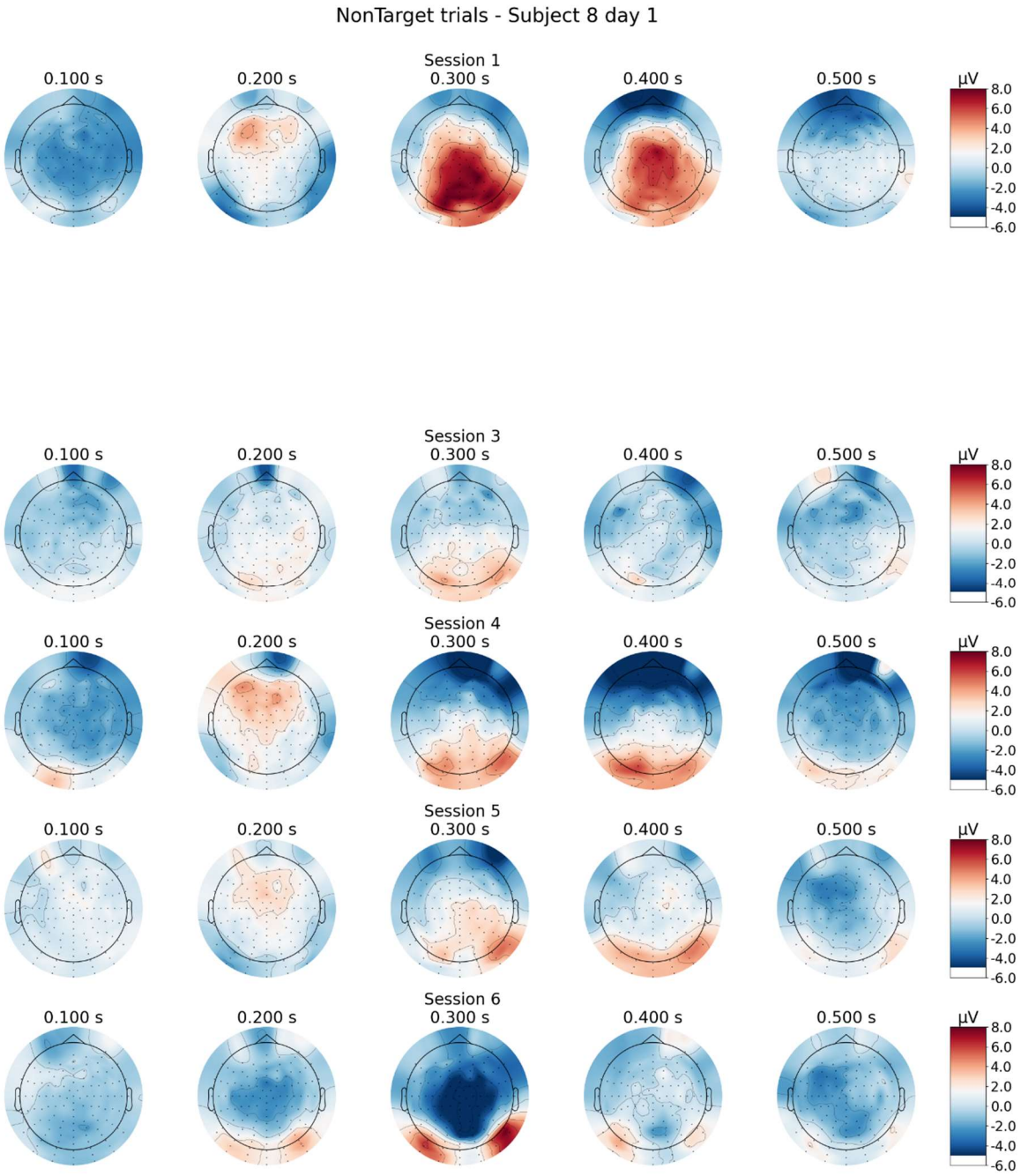


Figure 132: Topographic maps of event related potentials of Subject 8 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

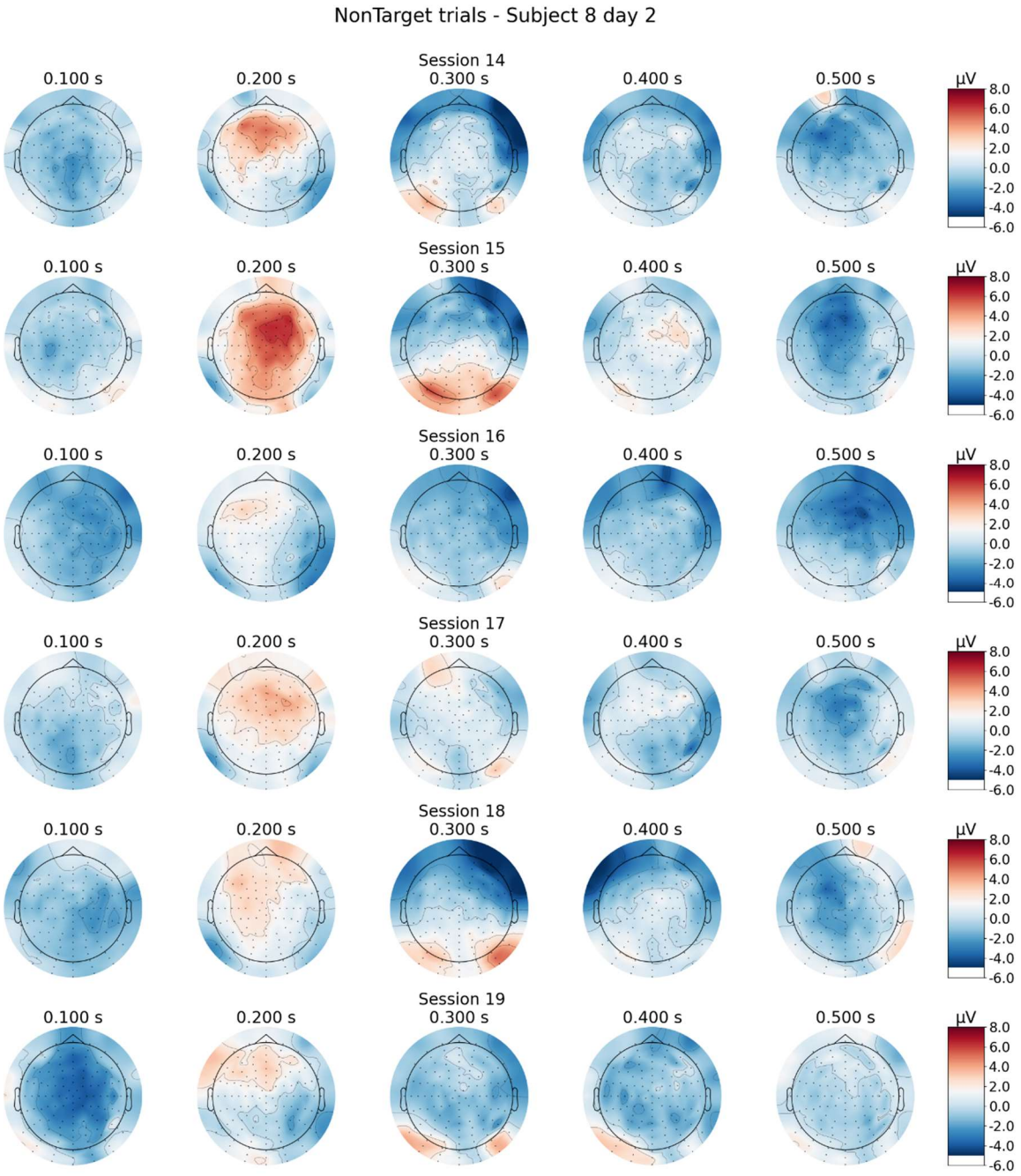


Figure 133: Topographic maps of event related potentials of Subject 8 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.9.3 Subject 9

Subject 9 was a 26-year-old right-handed female. Their questionnaire revealed that their game strategy did not change during the course of the study. They reported focusing on responding to Target stimuli rather than avoiding Non-Target stimuli. They reported prioritizing accuracy over speed. Their mean RT was 384.8ms (SD=30.5ms), mean accuracy to target trials was 96.0% (SD=8.4%), and mean accuracy to Non-Target trial was 99.4% (SD=1.0%). Behavioural data from Subject 9 are presented on Figure 134.

5.3.9.3.1 Questionnaire

	Subject
Which option best describes your strategy at the beginning of the first session	I was trying to shoot aliens rather than avoid astronauts
Which option best describes your strategy by the end of the last session	I was trying to shoot aliens rather than avoid astronauts
Can you remember if your strategy changed at some point during the study?	I did not change my strategy
If so, would you be able to say when?	N/A
Did any of the game features (such as points or bonus stars) impact your game strategy?	The number of aliens is much less than astronauts.
Did you prioritize speed over accuracy?	No
Did you prioritize accuracy over speed?	Yes
Did you prioritize speed and accuracy equally?	No

Table 28: Questionnaire data from Subject 9.

5.3.9.3.2 Behavioural analysis

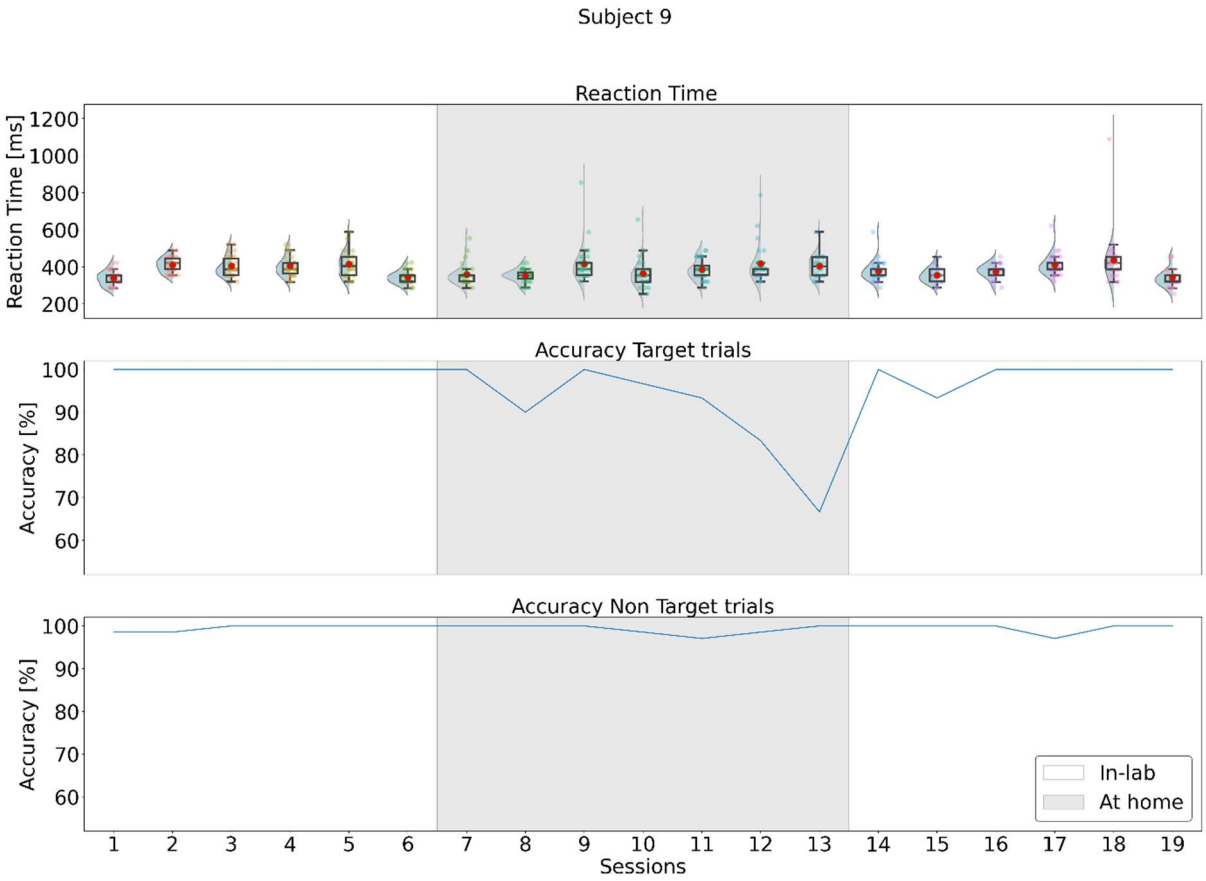


Figure 134: Behavioural responses of Subject 9. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.9.3.3 EEG analysis

EEG data of Subject 9 are presented on Figures 135 to 141. Both for Target and Non-Target trials, early sensory components can be observed between 0 to 250 ms, although it should be noted that their amplitudes is unusually large. No clear Target P300 signal may be observed during the first in-laboratory visit, while signals of low amplitudes may be observed in three gameplays during the second in-laboratory visit. Well defined Non-Target P300 signals are observed during the first in-laboratory visit but not during the second visit (Figures 136 to 137). For both conditions, the amplitudes of the signals seem to be maximal around fronto-central regions (Figure 135, and Figures 138 to 141).

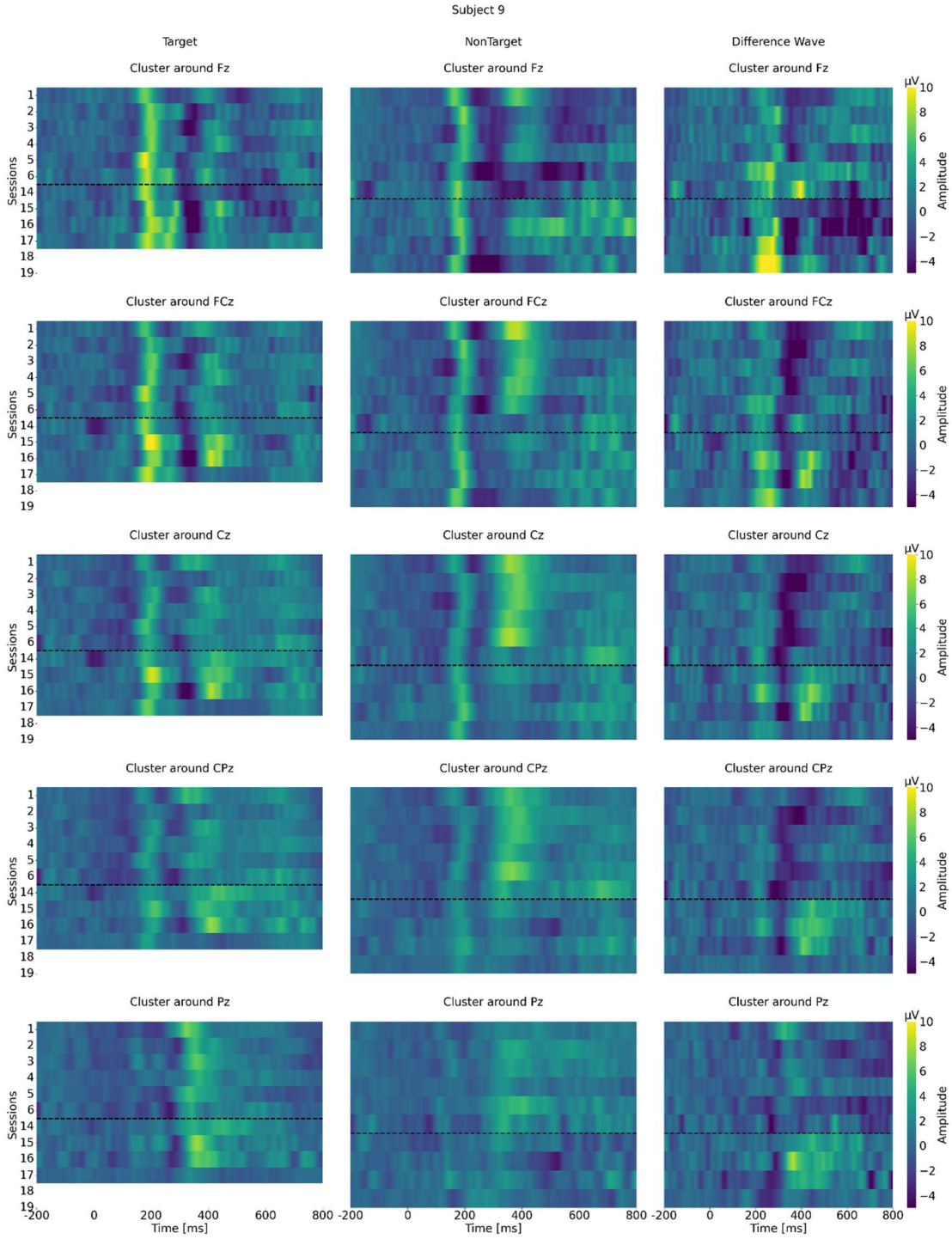


Figure 135*:* Mean event-related potentials for each session extracted around clusters of interest for Subject 9. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

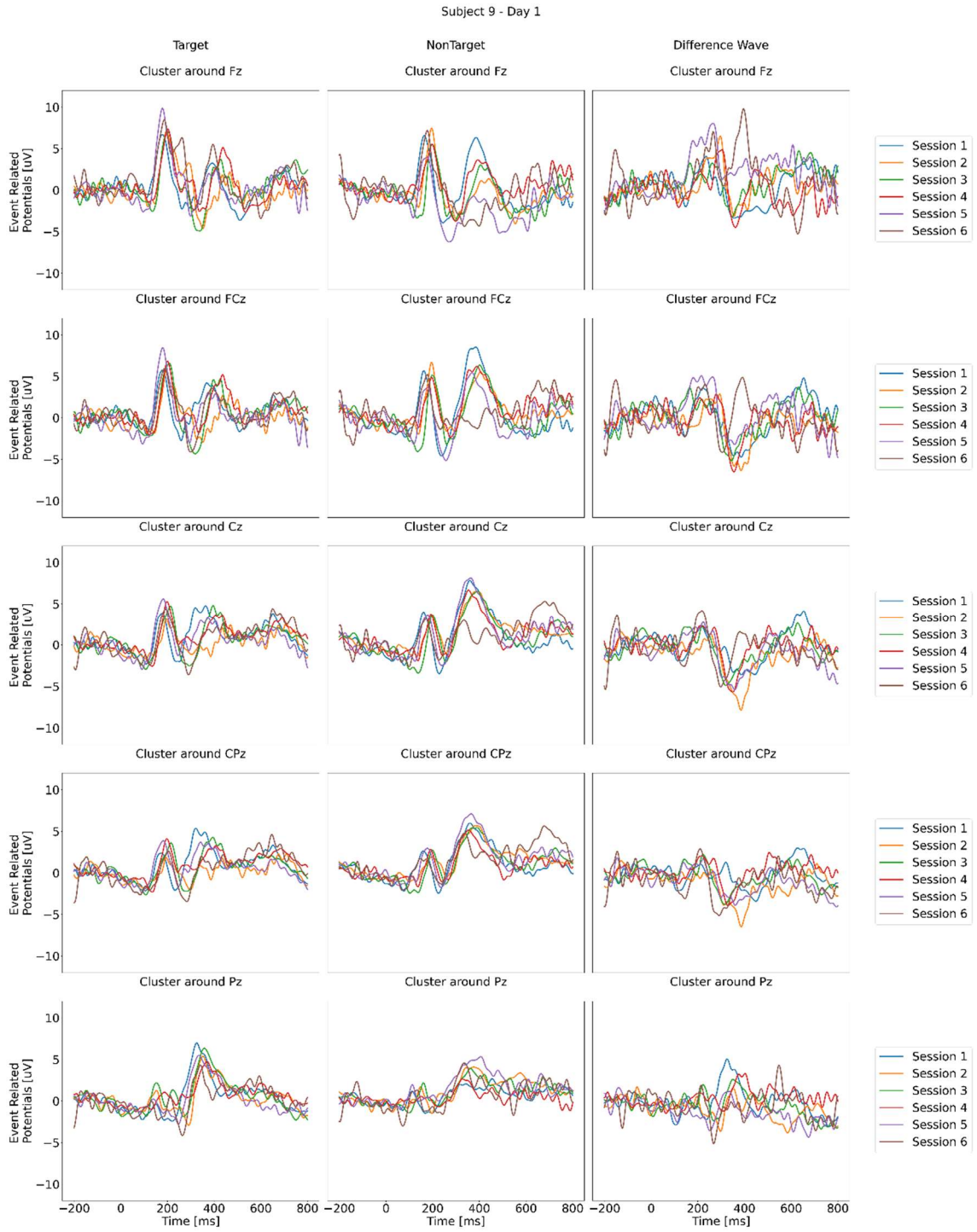


Figure 136: Event Related potentials traces around clusters of electrodes of interest for Subject 9 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

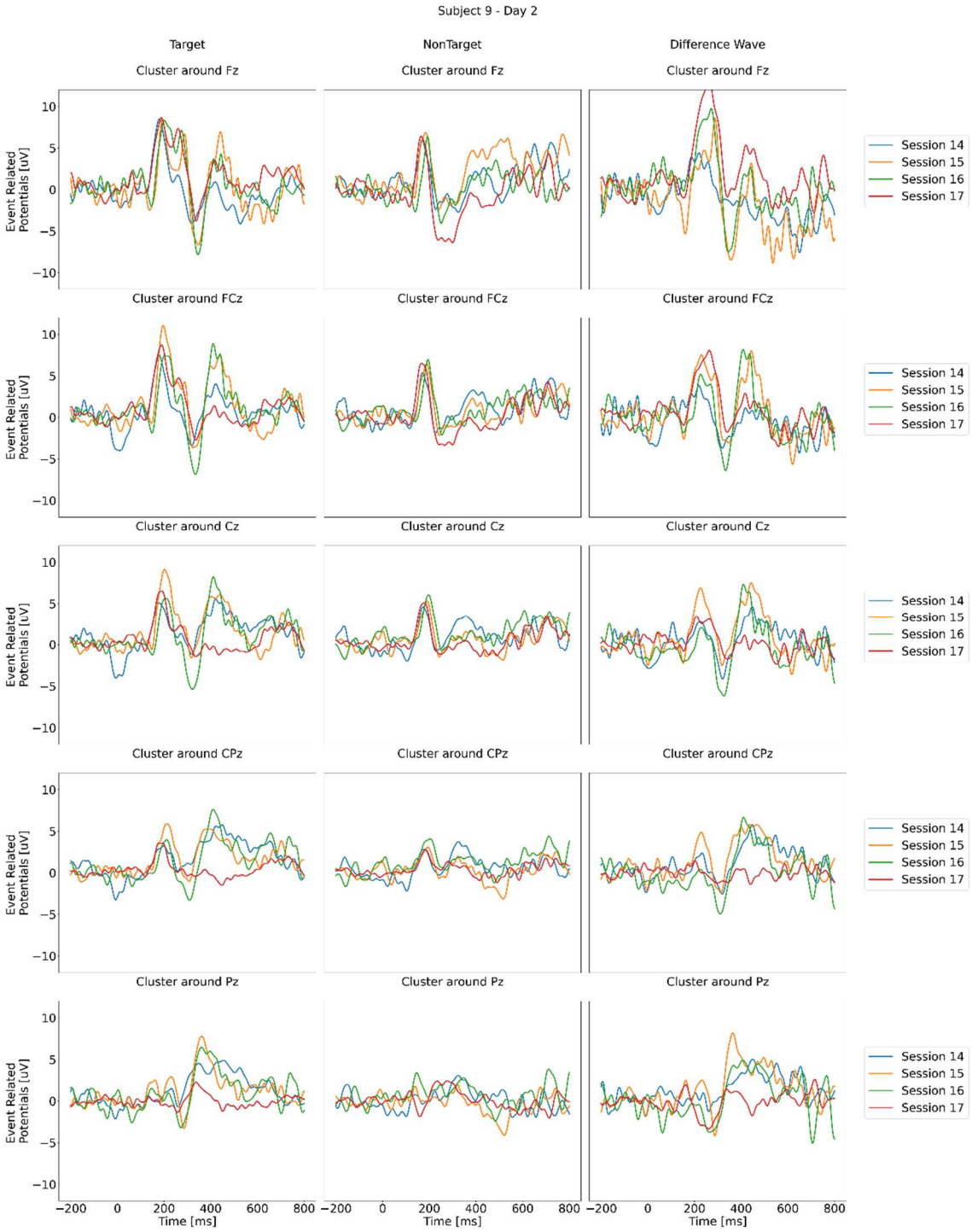


Figure 137: Event Related potentials traces around clusters of electrodes of interest for Subject 9 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

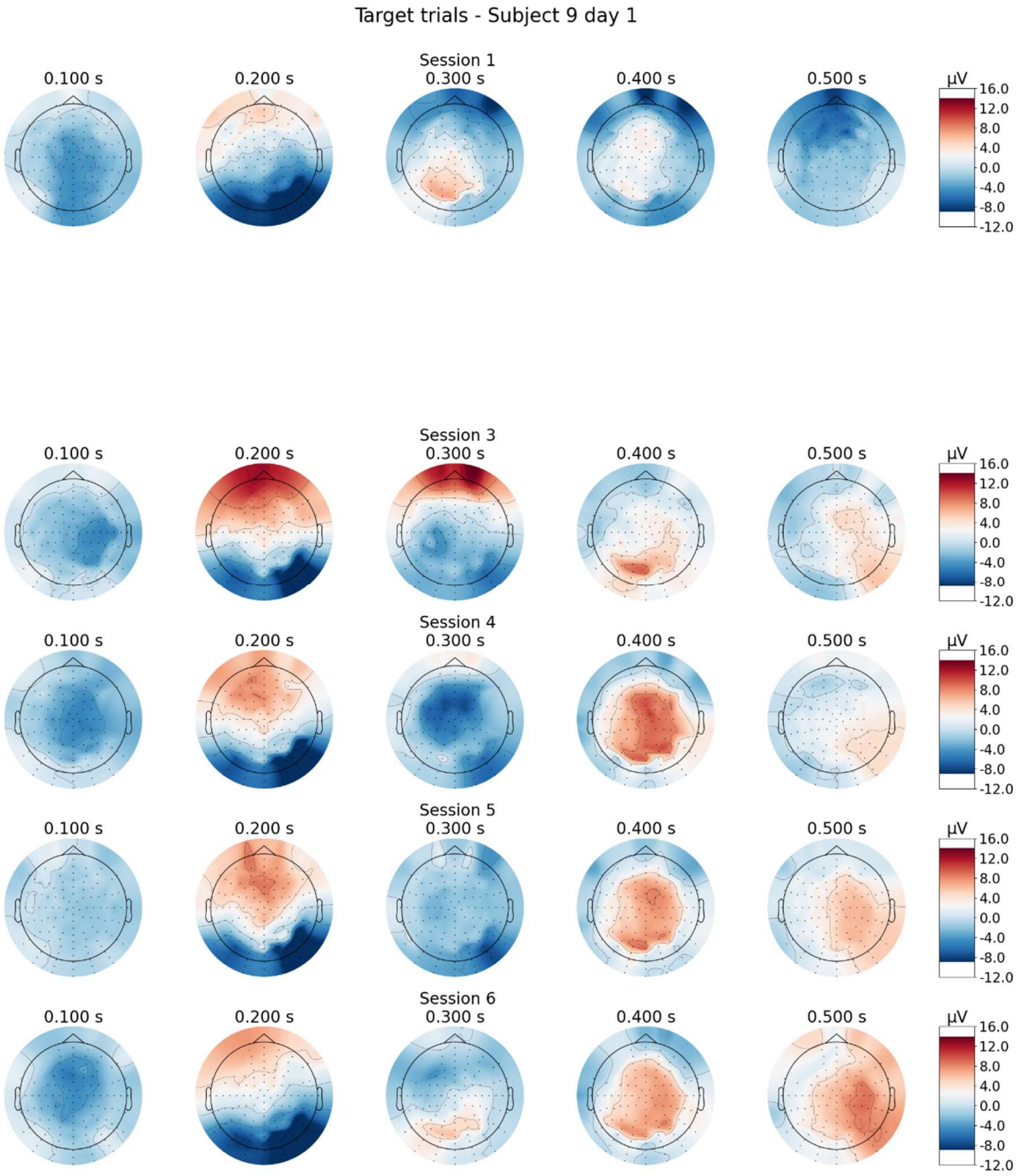


Figure 138: Topographic maps of event related potentials of Subject 9 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

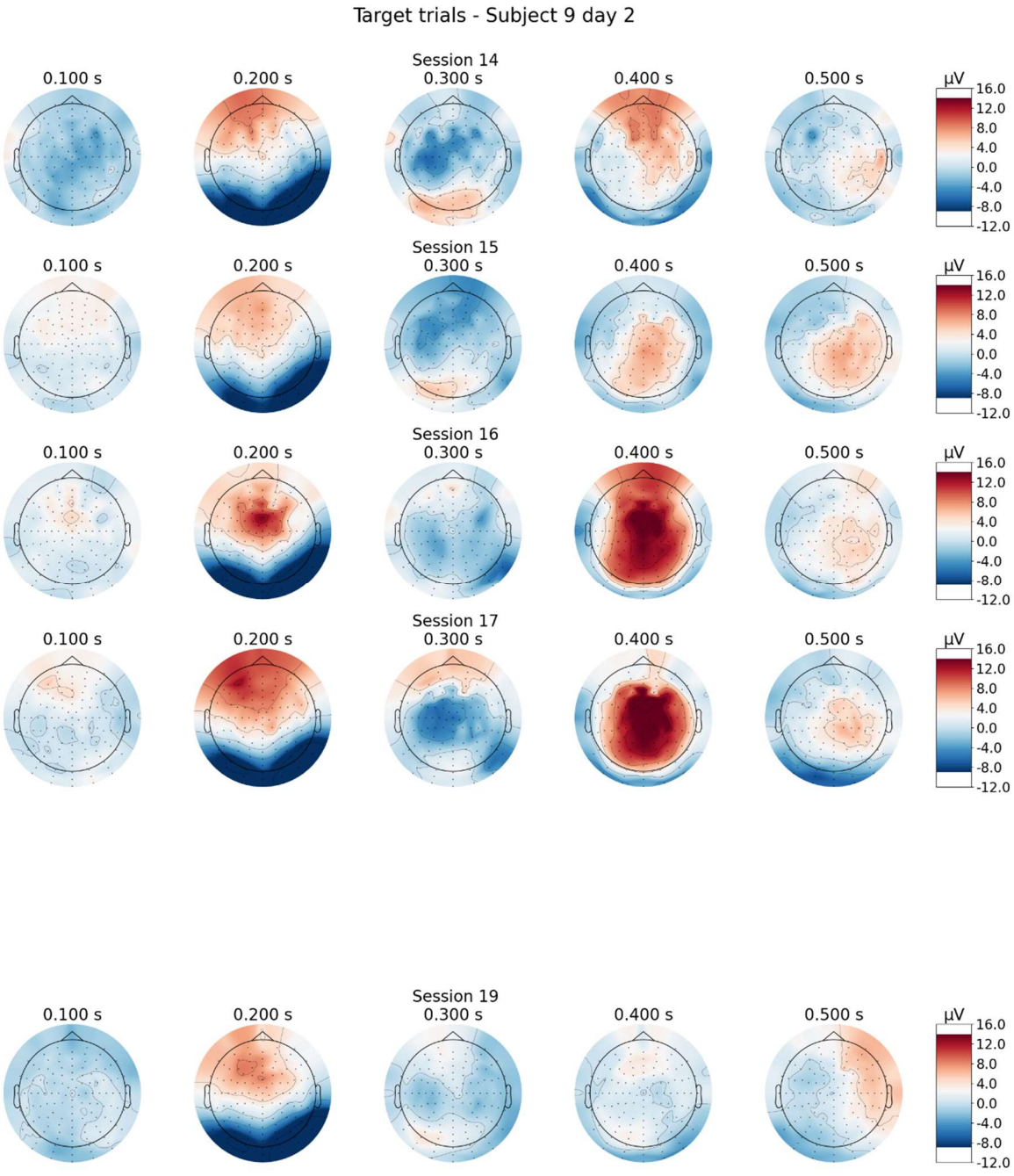


Figure 139: Topographic maps of event related potentials of Subject 9 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

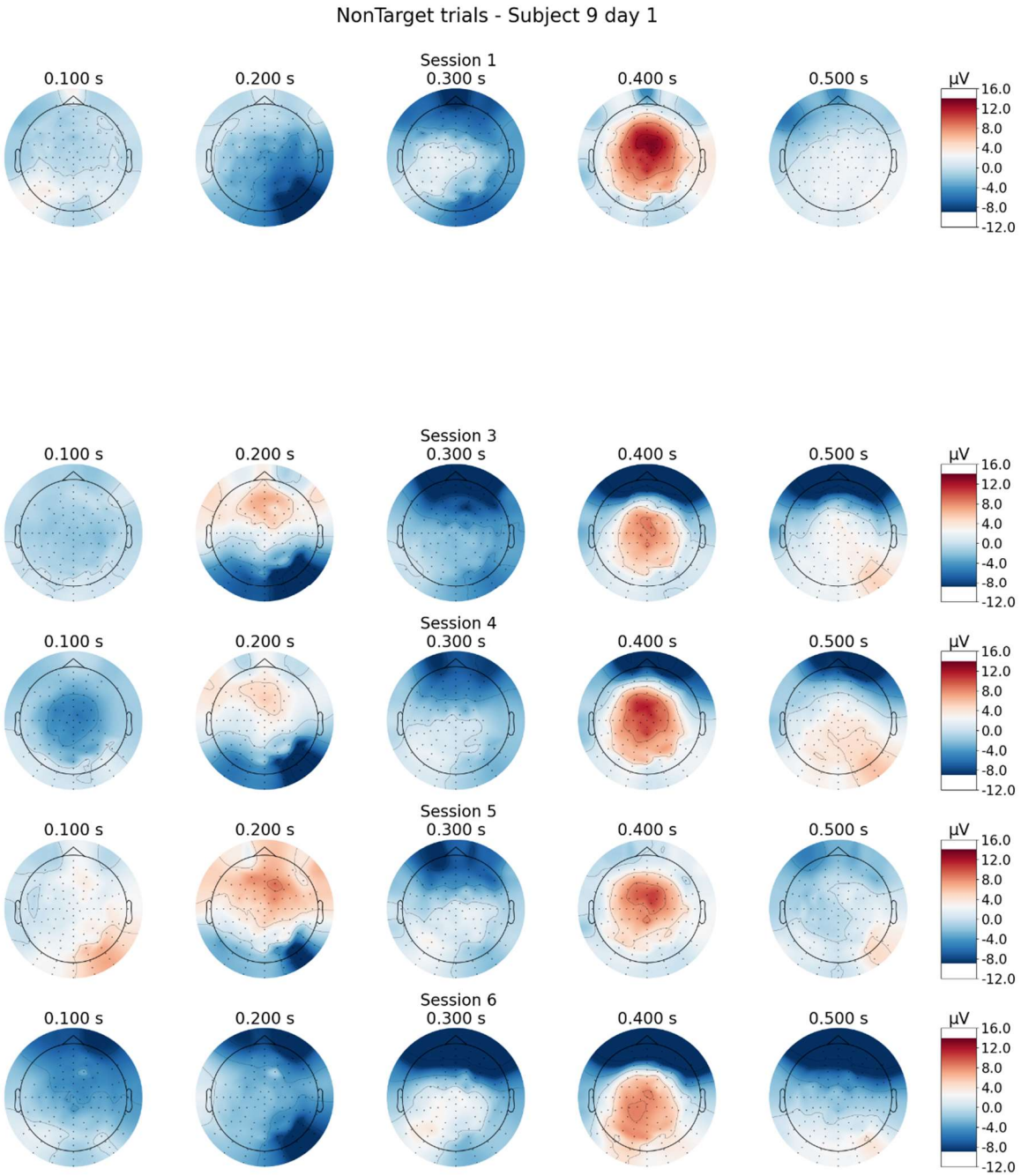


Figure 140: Topographic maps of event related potentials of Subject 9 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

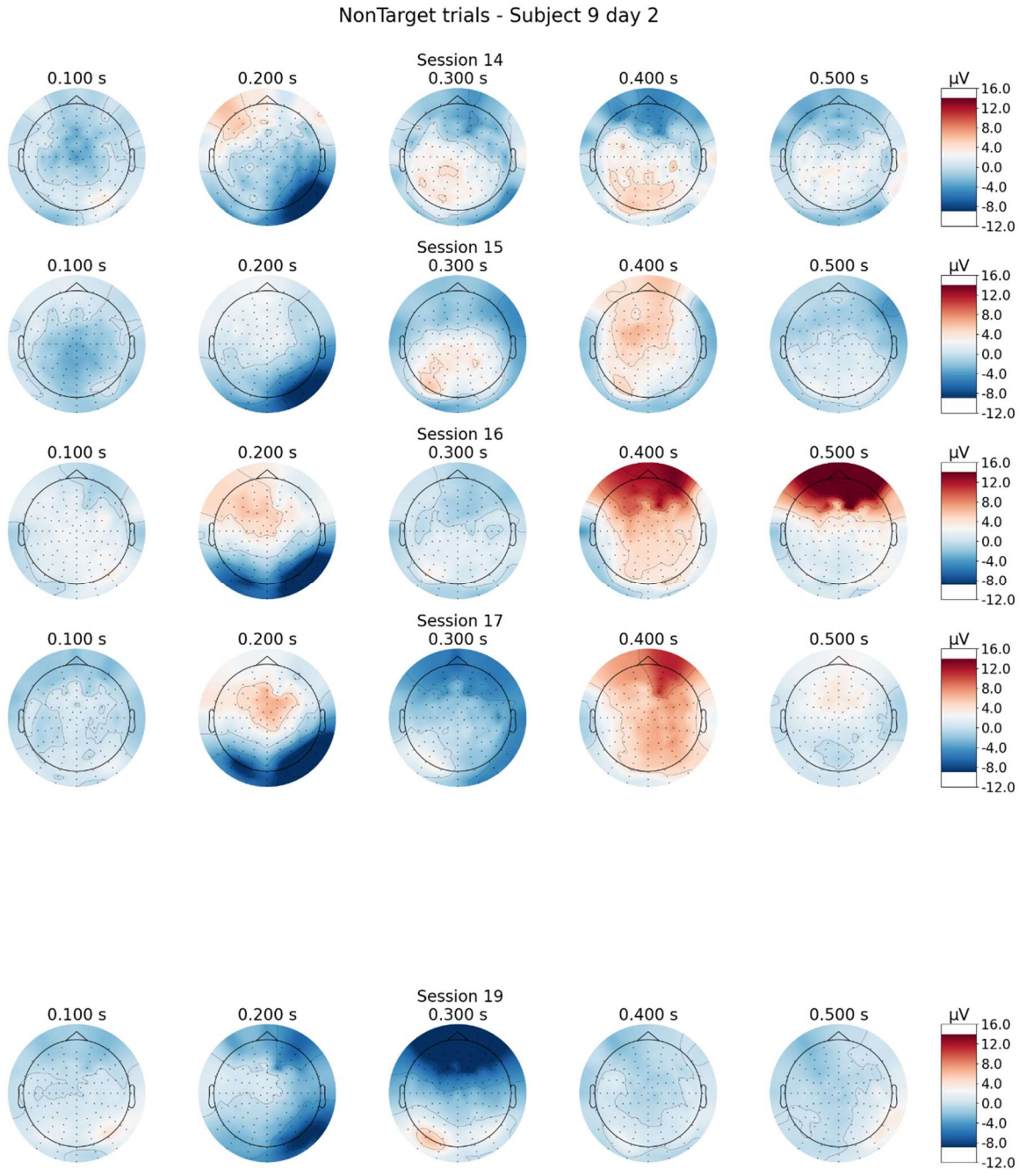


Figure 141: Topographic maps of event related potentials of Subject 9 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.3.9.4 Subject 10

Subject 10 was a 23-year-old right-handed male. Information on game strategy was not available as subject 10 did not send back their debrief questionnaire. Their mean RT was 348.2ms (SD=20.5ms), mean accuracy to target trials was 99.6% (SD=1.1%), and mean accuracy to Non-Target trial was 97.7% (SD=1.8%). Behavioural data from Subject 10 are presented on Figure 142.

5.3.9.4.1 Questionnaire

No questionnaire is available for subject 10 as they did not send back their questionnaire after the end of the study.

5.3.9.4.2 Behavioural analysis

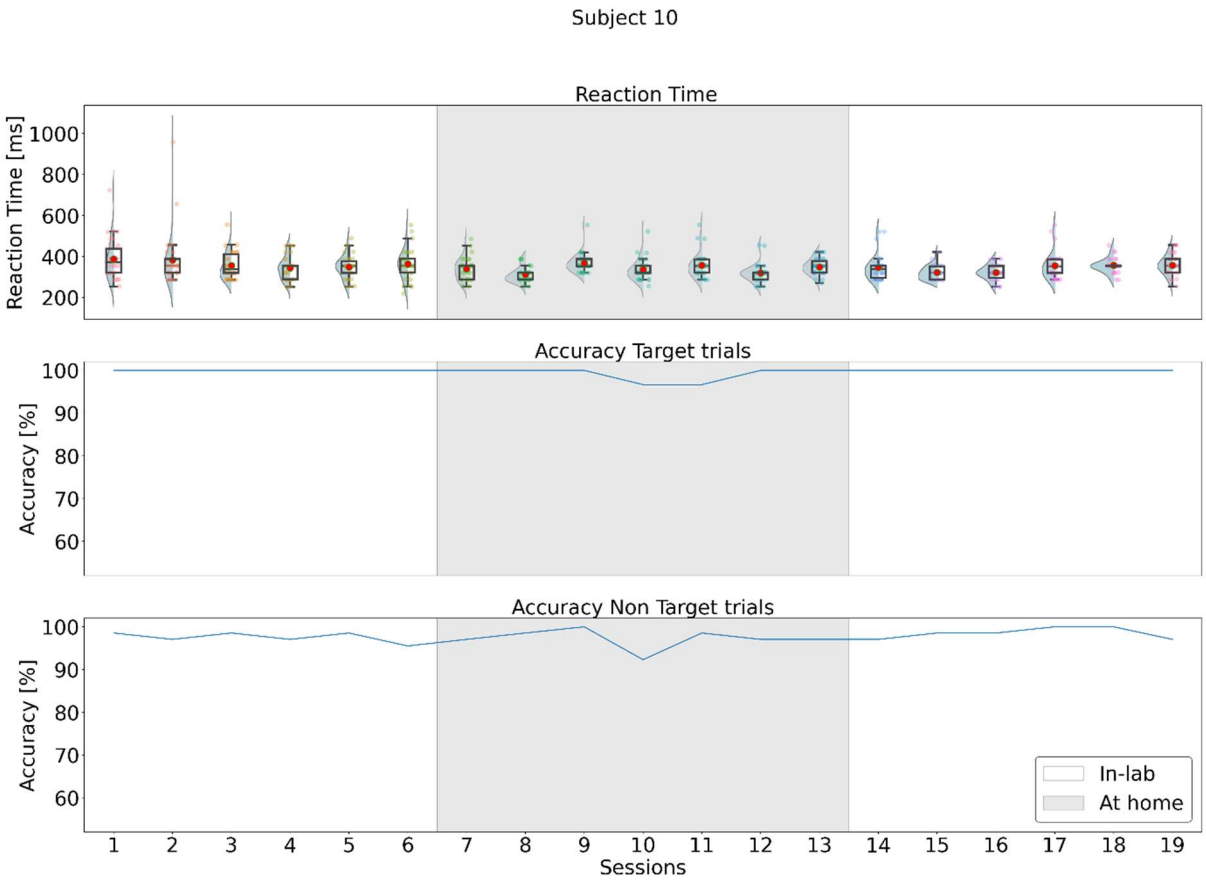


Figure 142: Behavioural responses of Subject 10. Top row: Reaction time to correct Target trials. Middle row: Accuracy to target trial. Bottom row: Accuracy to Non-Target trials. The shaded areas correspond to data collected remotely from the home.

5.3.9.4.3 EEG analysis

EEG data of Subject 10 are presented on Figures 143 to 149. Both for Target and Non-Target trials, early sensory components can be observed between 0 to 250 ms, although it should be noted that the signal amplitude is very small in several instances. When looking at ERP traces (Figures 144 and 145), no clear Target P300 or Non-Target P300 signal may be observed.

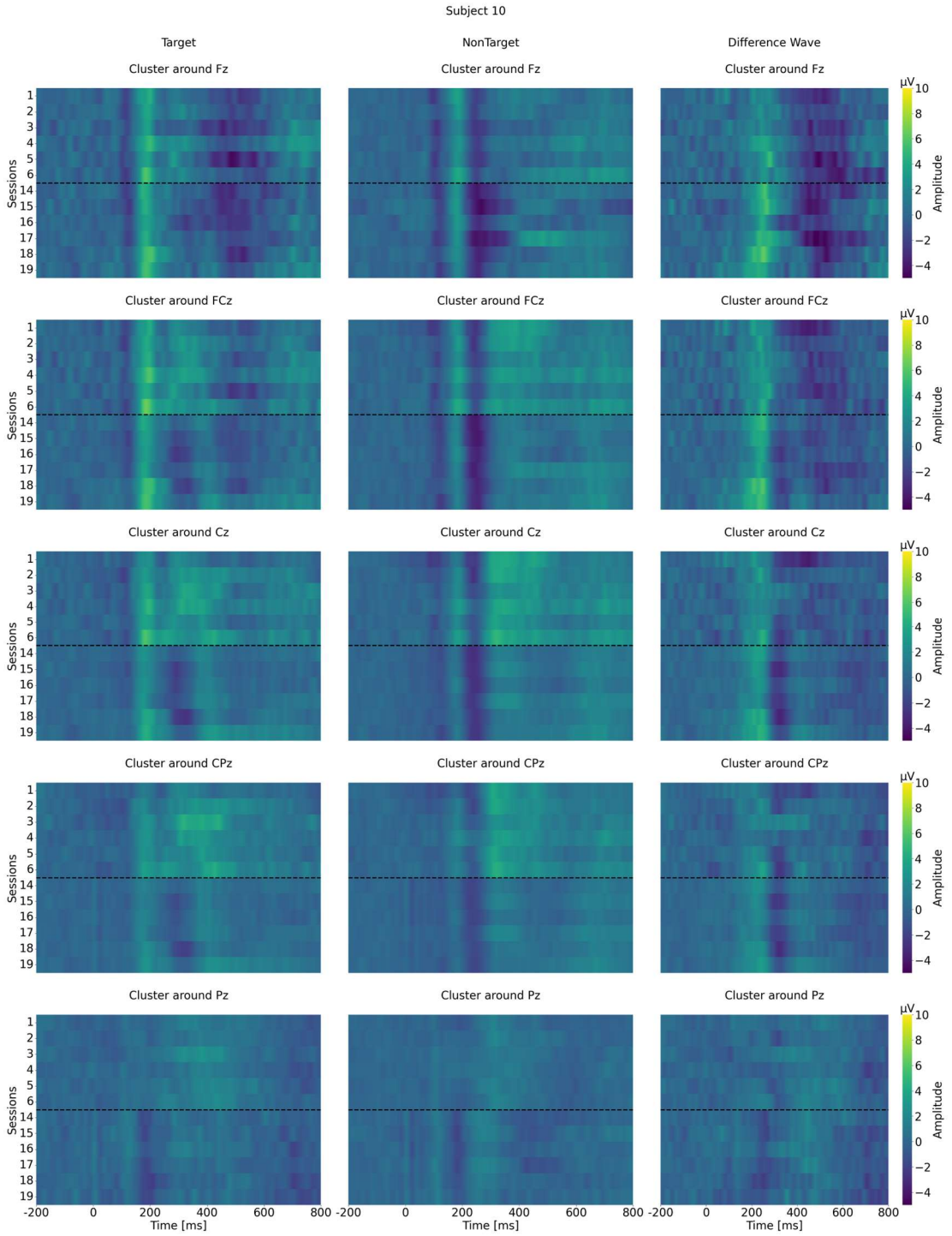


Figure 143: Mean event-related potentials for each session extracted around clusters of interest for Subject 10. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

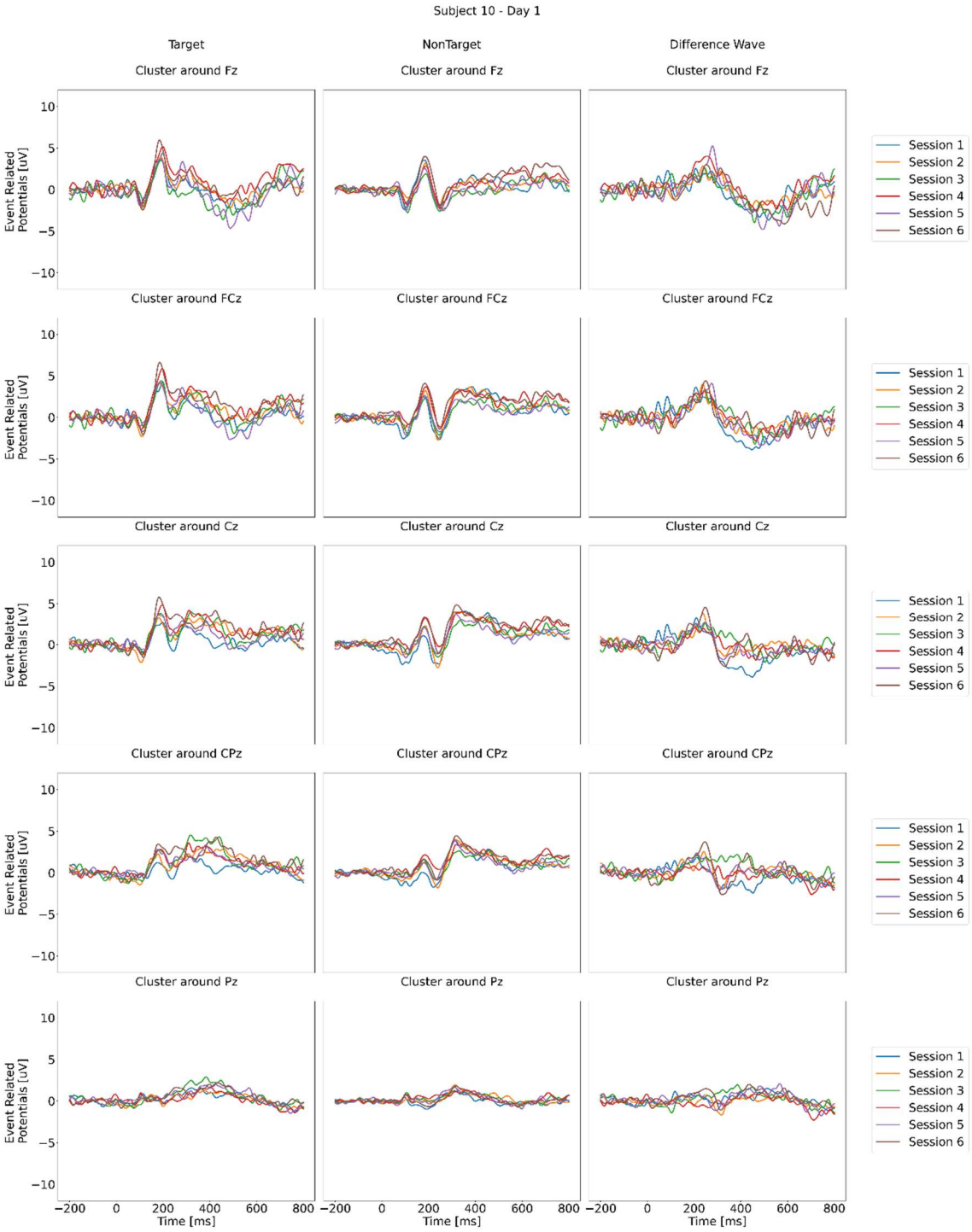


Figure 144: Event Related potentials traces around clusters of electrodes of interest for Subject 10 during the first visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

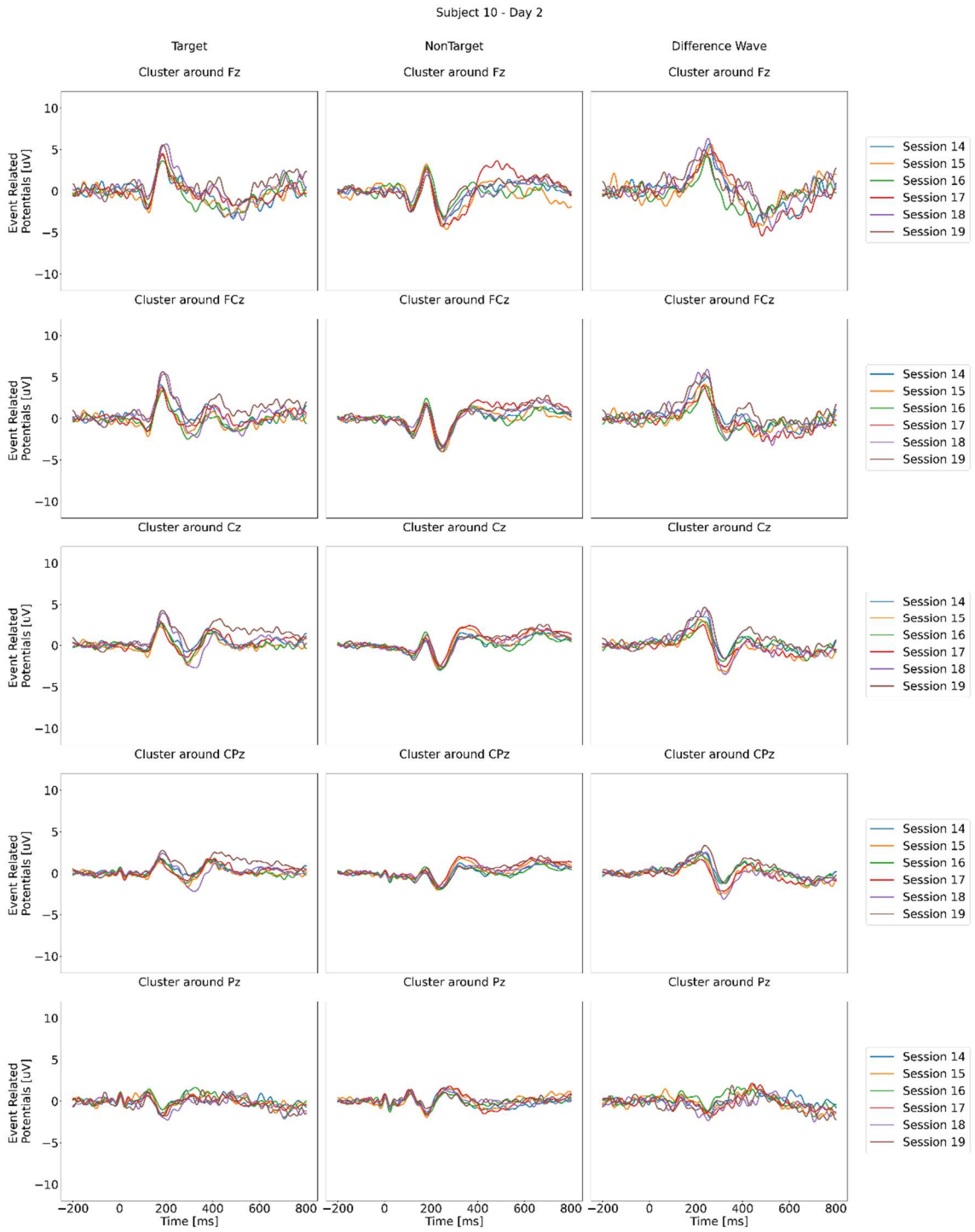


Figure 145: Event Related potentials traces around clusters of electrodes of interest for Subject 10 during the last visit in the laboratory. Each line of a plot represents a session. Each row of the figure represents a different cluster of electrodes. From top to bottom in order: Clusters around Fz, FCz, Cz, CPz, and Pz. The left column corresponds to Target trial, the middle column to Non-Target trials, and the right column to the difference wave between Target minus Non-Target trials.

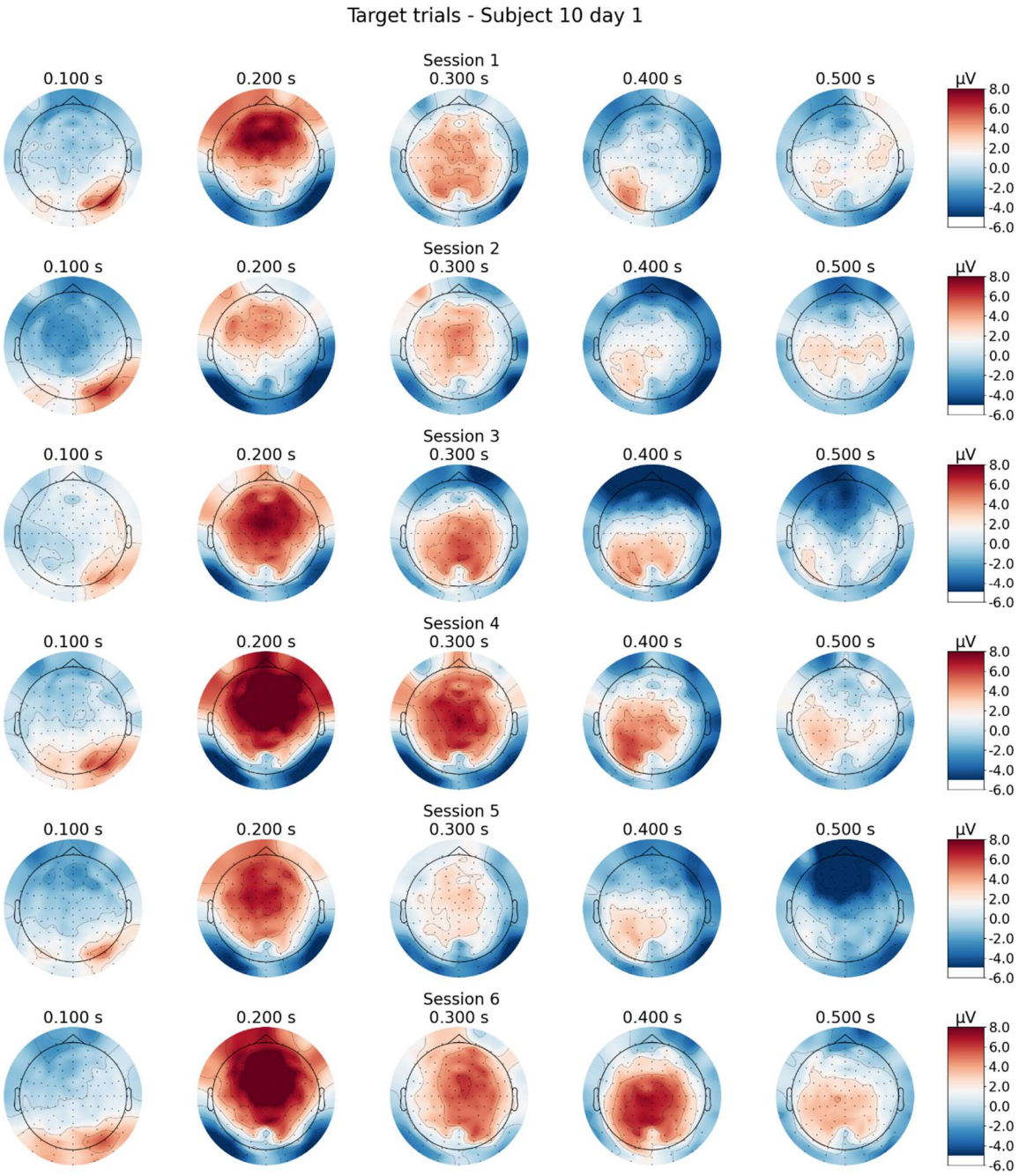


Figure 146: Topographic maps of event related potentials of Subject 10 to Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoint. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

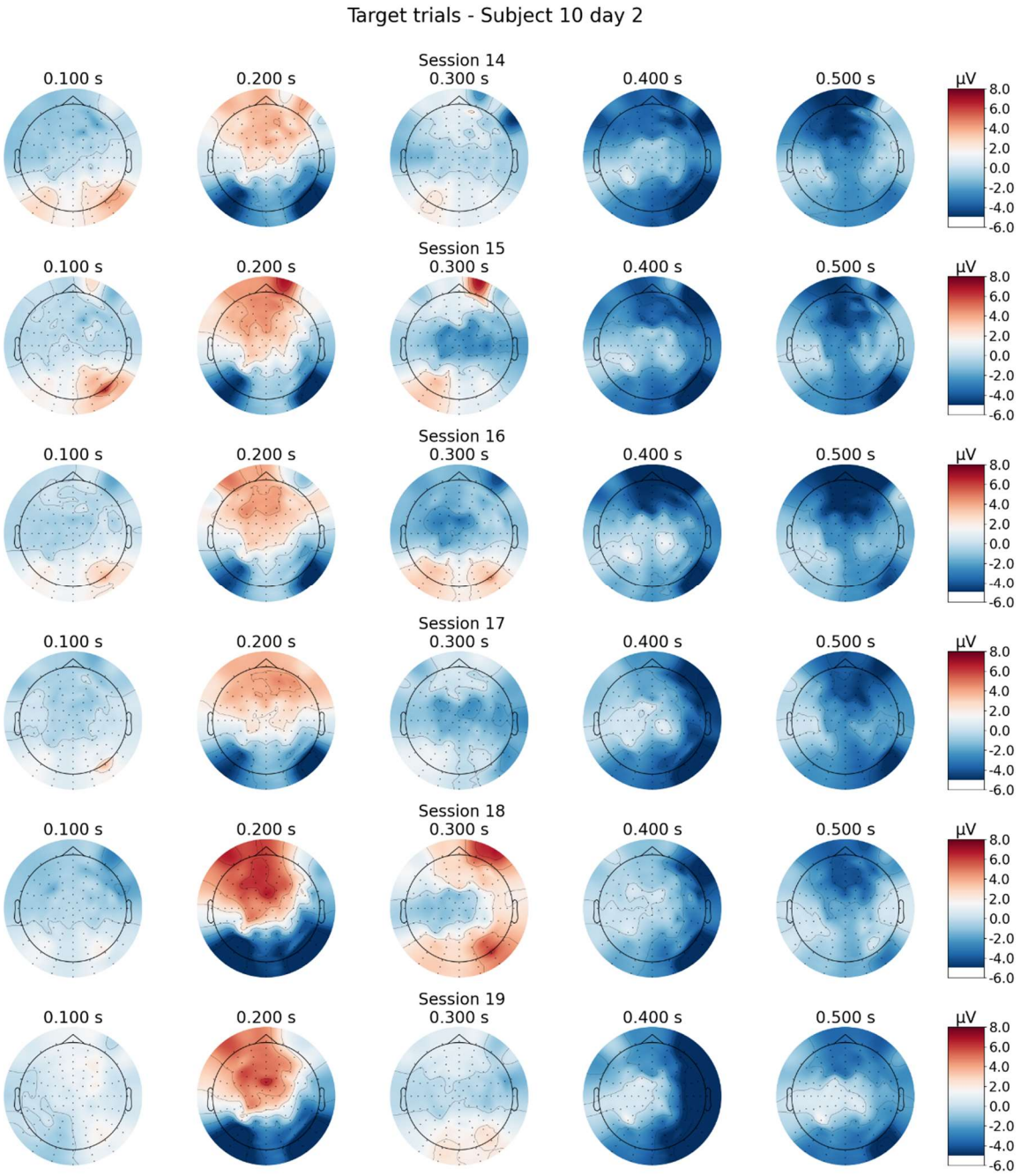


Figure 147: Topographic maps of event related potentials of Subject 10 to Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

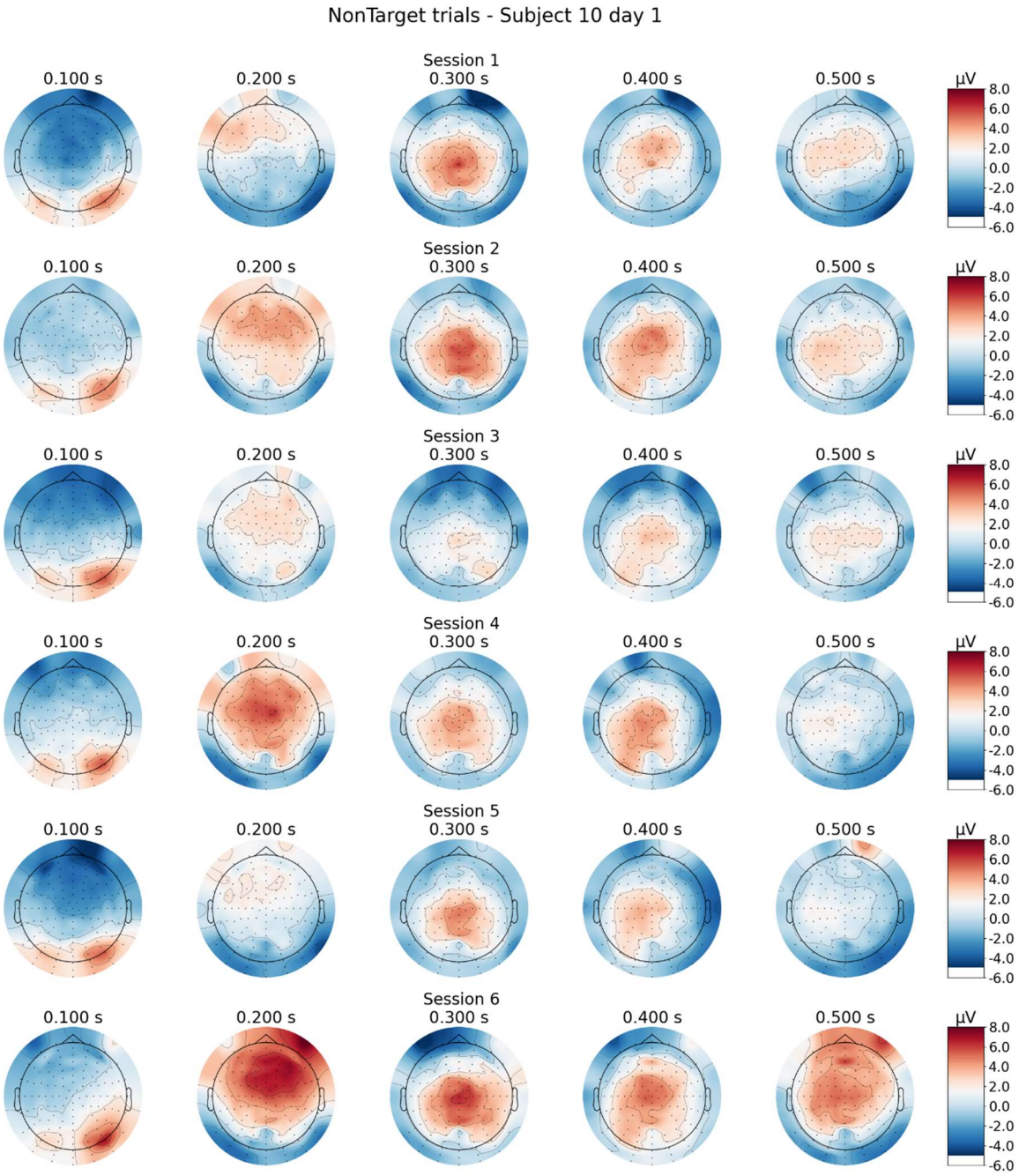


Figure 148: Topographic maps of event related potentials of Subject 10 to Non-Target trials during the first visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

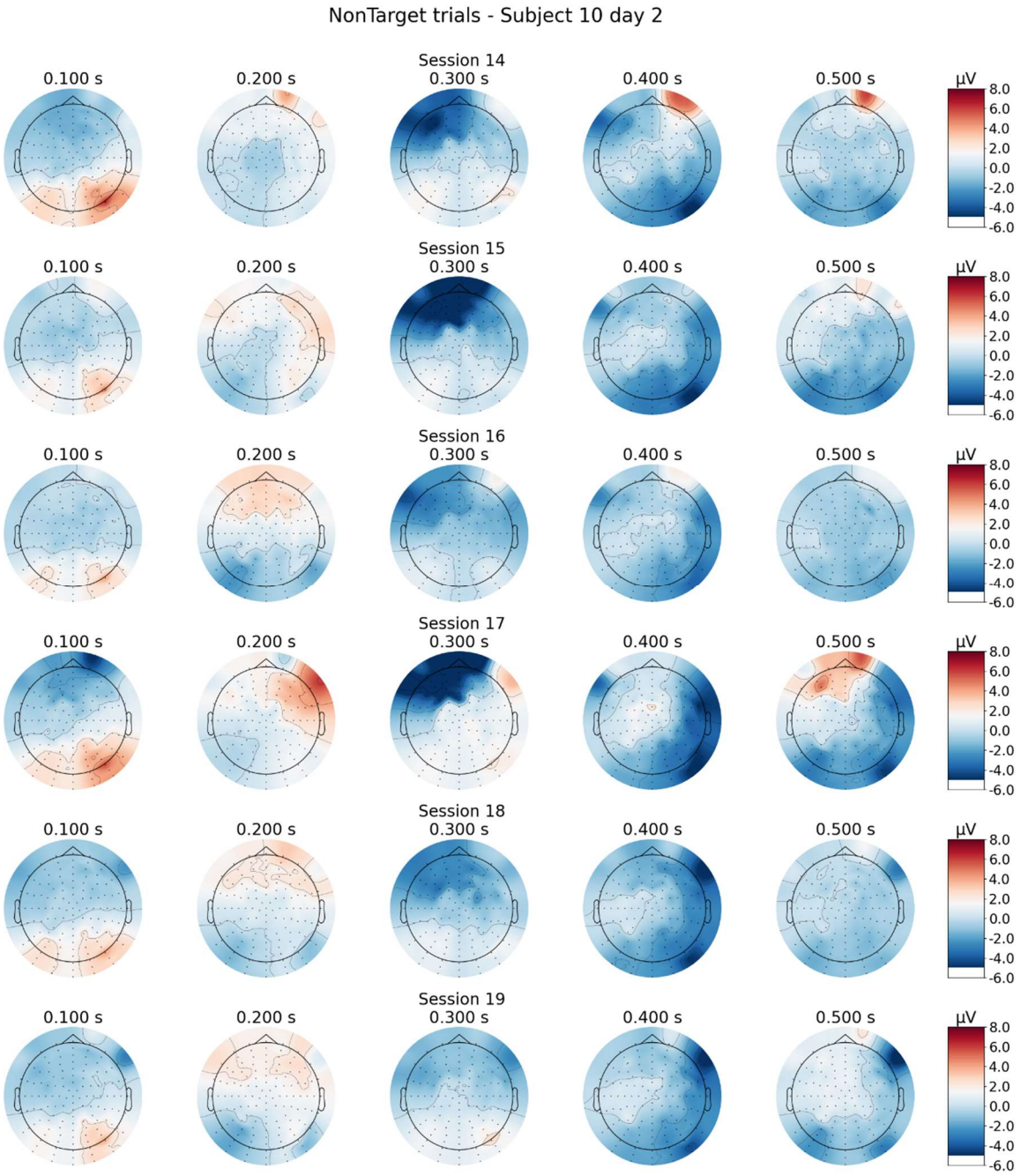


Figure 149: Topographic maps of event related potentials of Subject 10 to Non-Target trials during the last visit in the laboratory. Each line corresponds to a different session, each column to a different timepoints. From left to right, topographic maps at: 0.1s, 0.2s, 0.3s, 0.4s, and 0.5s after Target stimulus presentation.

5.4 Discussion

The objective of this study was to evaluate the construct validity of a gamified cognitive task to elicit a well-established and widely used ERP, the P300. We collected multiple wet EEG samples from a young healthy cohort in the laboratory under researchers' supervision. For all participants and trial conditions, we observed the expected ERP features which included early perceptual sensory components followed by the P300 signal. Game strategy varied across participants with equal numbers of people prioritizing either speed or accuracy.

I briefly describe the main results here. The broader implications of these results are discussed in section 6.2.3 of the general discussion. Behavioural data analyses revealed reaction times within the expected range, that is between 300 to 400 ms. Ceiling effects were observed in both the Target and Non-Target conditions with both yielding accuracy values over 98%. The topography of the ERPs varied per conditions. The results for Non-Target trials were consistent across participants. All exhibited quite clear frontocentral or central distribution of the signals. This result was unexpected and invalidated our initial hypothesis that Non-Target trials would be maximal over centro-parietal regions. It is a surprising finding as frontocentral distributions are usually associated with inhibitory processes and Nogo P300 (Salisbury *et al.*, 2004; Smith, Johnstone and Barry, 2006; Albert *et al.*, 2013). This result suggests that unanticipated cognitive functions may have been recruited instead of or in addition to the ones initially targeted. Target trial topographies were more mixed with four participants exhibiting the expected central and centro-parietal signals while Subject 2 exhibited a bilateral pattern. It is unclear what could be the reason for such a pattern, but a potential explanation could be that motor artefacts contaminated the recordings. Finally, the topography of Subject 6 seemed to move from frontocentral to centroparietal regions throughout the course of the study. This shift in topography is also an unexpected finding and may suggest that the participant engaged different cognitive functions during the course of the study.

When looking at the signal amplitudes, four subjects exhibited Non-Target ERP amplitudes that were larger compared to Target ERP amplitudes. Consequently, the grand average ERP peak amplitude of Non-Target trials across all subjects was higher compared to the Target trials. Finally, a general decrease of the signal amplitudes was also observed across time in four participants and in the study grand average of the Non-Target P300. These results were again unexpected and further support the hypothesis that different and/or additional cognitive functions may have been recruited during Non-Target trials compared to the task design intended to target. This point is further discussed in section 6.2.3 of the general discussion.

6 General Discussion

6.1 Summary of findings

The purpose of this thesis was to characterize the feasibility and validity of wireless dry EEG technology combined with gamified paradigms to repeatedly and remotely sample brain activity and cognitive functions. To do so, three studies using a variety of experimental and analysis methods were presented. These empirical chapters investigated: i) the quality of brain data when recorded outside the laboratory without supervision, ii) if dry EEG technology combined with gamified tasks could emulate results from the wet literature in a pharmacological use-case study, and iii) the validity of a gamified paradigm to elicit a well characterized ERP, the P300.

6.1.1 Empirical chapter 1

The first empirical chapter was aimed at evaluating the validity of the platform when used in the home by participant without supervision. My analyses were two-fold. Firstly, I evaluated the usability and feasibility of the technology using the participants' adherence to the protocol, successful data collection rate, and subjective reports. Secondly, I evaluated the quality of the data collected. More specifically, my analyses were aimed at gauging if wireless dry EEG recorded in the home with gamified cognitive tasks by participants without supervision could yield datasets of the same quality as published results derived from wet EEG recorded by an expert group in a controlled environment. I conducted post-hoc quality analyses of dry EEG datasets recorded outside the laboratory for other purposes. The primary findings of Empirical Chapter 1 were that 1) participants reliably collected EEG data on a near-daily basis and 2) it was possible to obtain a similar level of signal quality using a dry EEG system, compared to wet EEG, when comparing populations of similar age. However, the percentage of trials discarded after artefact rejection was substantially higher in the dry system versus the wet EEG reference study. Consequently, aggregations of multiple sessions (2-3, depending on task) were performed to obtain grand

average signal quality comparable to that of single-session data collected by experts in a laboratory setting using wet EEG. Participants reliably collected EEG data on a near-daily basis.

6.1.2 Empirical chapter 2

In the second empirical chapter, I deployed the gamified dry EEG technology in a ketamine challenge study performed in 30 healthy volunteers and evaluated if data collected in and outside the laboratory could emulate results from the wet literature. I targeted well-established EEG-derived signals including the mismatch negativity (MMN), gamma- and alpha-band power modulations, as well as other electrophysiological markers that have been associated with the ACC and PFC activity (e.g., the ERN and P300). The in-laboratory data collected with the dry EEG platform only partially emulated the wet EEG literature. The well-described gamma enhancement during the ketamine infusion was observed, but no other analyses yielded significant results. Other important factors unrelated to the technology itself, such as the timing of the sessions and the drug dosage may have contributed to the lack of significant results. After that in a second set of analyses, I evaluated, for the first time, multiple timepoints collected during the week after a ketamine intervention in a healthy cohort. This data collected from the home also did not yield any significant results, despite using multi-session aggregates in the statistical analyses. These results suggest that the effects of ketamine on EEG signals may not persist in the days after the intervention in a male only healthy cohort.

6.1.3 Empirical chapter 3

Finally, our last set of analyses was aimed at exploring the effect of task gamification on the elicitation of one of our ERP of interest: the P300. A growing number of laboratories are now using gamified cognitive paradigms to evaluate a wide range of cognitive functions including working and episodic memory, executive functions, and inhibitory mechanisms. However, this technology has not yet been used in conjunction with EEG to elicit ERPs. In this study, I evaluated the ability of a gamified task to elicit the P300 ERPs associated with decision-making and context-updating mechanisms. Healthy controls were recruited from the local community and completed repeated

recordings of a gamified visual Oddball task either in the laboratory or from the home. When sessions were completed in the laboratory, wet EEG was recorded simultaneously to evaluate the brain signals elicited by the gamified paradigm. My analyses revealed that the evoked ERPs had similar latencies, morphologies, amplitudes, compared to the extant literature. Target trials signals exhibited the classical features of a P3b component. However, the topographies of Non-Target trials were more anterior than anticipated and may be more akin to inhibitory-related ERPs signals than traditional Non-Target signals. It is possible that gamification features impacted the nature of cognitive functions at play during the task. Nonetheless, I observed well defined ERPs with broadly consistent morphologies and timings across all participants. These results suggest that gamified cognitive paradigms can elicit reproducible ERPs.

6.2 General discussion

6.2.1 Remote EEG feasibility and variability

Analyses conducted in *Empirical Chapter 1* provided valuable insights into how to best deploy portable dry EEG technology outside the laboratory to collect resting state and ERPs data of sufficient quality to conduct clinical research.

First, usability analyses revealed no clear evidence of a usability barrier in the older cohort as attested by the lack of differences in usability scores between the two groups. This result is in agreement with findings from Nicosia and colleagues who reported that, while older age is associated with less technology familiarity, older adults are willing and able to participate in technology-enabled studies (Nicosia, Aschenbrenner, Adams, *et al.*, 2022). The high percentage of successful sessions in the older cohort also underlines that the ease-of-use of the platform was satisfactory and enabled populations who were not digital natives to use the system. Notably, there was no substantial drop in adherence during later phases of the studies. These results are consistent with previous findings from McWilliams and colleagues who deployed the same dry

EEG technology in a separate cohort of 89 healthy older adults (40 to 80 yrs) and reported high adherence and usability scores (e.g., mean adherence of 82% and mean SUS score of 78.7) (McWilliams *et al.*, 2021). Our compliance levels are also slightly higher than those observed in purely behavioural remote studies using smartphone for repeated testing (e.g., adherence of 85.7% (Nicosia, Aschenbrenner, Adams, *et al.*, 2022)). As discussed by Moore et al., it is likely that our older participants' high adherence rate is due to a combination of extrinsic factors including the ease-of-use of the technology, and intrinsic factors such as personal motivation (the older cohort self-referred into our study) (Moore *et al.*, 2021). No carer or study partner attended the initial in laboratory on-boarding visit suggesting that a single in-person training session was sufficient for older adults to commence at home recording. However, I do not know if participants were helped by another person once in the home. Further, clear differences in data quality were noted between the younger and older groups. On average, data quality was lower for older adults with more data rejected and more failed sessions in the home. These results suggest that thorough usability and validation analyses will have to be completed in different cohort and clinical populations of interest before deploying this technology in clinical trials. It is possible that populations suffering from cognitive and/or motor impairments will need additional assistance and/or to collect more sessions to reach similar level of data quality.

When comparing the dry datasets with a wet EEG dataset collected during single sessions in the laboratory under researcher supervision, my analyses revealed that between 2 to 3 at-home gamified dry EEG sessions using the same tasks parameters would yield the same SMEs as the wet EEG system for comparable cohorts. Future studies should aim at collecting multiple sessions at timepoints of interest so that several sessions could be aggregated and evaluated together. One can imagine that longitudinal study design will need to include bursts of sampling; for example, a week of recordings, occurring at regular intervals throughout the clinical trials to optimize data collection. Our analyses showed that multiple factors impacted data quality. Headset type, task gamification, age, openness of the participants to the technology, platform usability and

researcher supervision all likely played a part in the final quality of the datasets collected. The main factor guiding the decision of how many trials should be collected in traditional in-clinic wet EEG studies is the quality and variability of the signal. The burden of the tasks is a secondary concern. Indeed, as participants are in the laboratory once or twice only and as the hardware can be cumbersome to configure, researchers aim to collect as many trials as possible in the shortest amount of time. When designing tasks for repeated self-administered measurements in the home, the recordings need to be short and enjoyable enough so that participants are inclined to conduct additional sessions (Lumsden *et al.*, 2016). Thus, considering this factor combined with the fact that dry EEG data are inherently noisier than wet data because of the dry electrode higher impedance, it is unsurprising to find that one must aggregate over a number of sessions to reach equivalent quality levels. These observations are also consistent with behavioural findings from studies evaluating online platforms and mobile-apps (Crump, McDonnell and Gureckis, 2013; Shapiro, Chandler and Mueller, 2013; Chandler and Shapiro, 2016a; Chandler and Paolacci, 2017; Lipsmeier *et al.*, 2018; Coughlan *et al.*, 2019). For example, Lipsmeier and colleagues were able to distinguish healthy controls from individuals with Parkinson's disease by aggregating sensor-based features collected from mobile phones over 14 days (Lipsmeier *et al.*, 2018).

While it is tempting to conclude that more frequent sampling will totally compensate for the lower quality of remote data, the literature informs us that an increased rate of data collection must be implemented wisely. Increased data collection raises the burden put on participants and may negatively impact recruitment (Kerr *et al.*, 2019), drop-out rates (Gilliss *et al.*, 2001), and data quality (Musthag *et al.*, 2011). Thus, additional methods improving data quality as well as data quantity will have to be explored to optimize performance. *Empirical Chapter 1* and *Empirical Chapter 3* revealed potential avenues to explore to improve data quality. Specifically, a possible strategy to reduce data variability without increasing participants time commitment and burden could be to reinforce task instructions. Both *Empirical Chapter 1* and *Empirical Chapter 3* revealed some heterogeneity in participant game and task strategies. Another approach could consist in

including a study partner or carer in the trial to support the participants. This may be particularly important in the case of patients suffering from motor impairments. Headset placement requires people to lift their arms and hands above their hand which may be difficult for people with reduced mobility. In this instance, if the person cannot manage to set the headset themselves in the first place, collecting multiple sessions will not improve data quality. Further, invaluable information could be gathered from study partners regarding the weaknesses of the method and how to improve it. Additional operational approaches will have to be implemented and tested in the field to maximize the integration of a partner efficiently. Research have up to now being centred around the patients and/or the target population that we want to study but studies around the role of a study partner in decentralised clinical trials could be of great interest when looking at ways of improving clinical trial operations.

6.2.2 Evaluation of the ketamine intervention

The characterization of gamma band modulation by ketamine in *Empirical Chapter 2* is a significant achievement as it demonstrates that self-administered dry EEG technology can accurately capture the effects of a drug targeting the central nervous system in a similar fashion compared to what is achieved with the gold standard wet EEG technology. Ketamine is currently examined as a potential therapeutic agent for a wide range of psychiatric disorders including MDD, anxiety, and PTSD. In 2017, 4.4% of the world population suffered from depression (>300 million people) and 3.6% of it (264 million people) had a diagnosis of anxiety disorder (WHO, Global health Estimates). Gamma-band alterations have previously been described in MDD, Bipolar Disorder (BP), and linked to the observed excitation: inhibition imbalance in the aforementioned disorders (Gilbert and Zarate, 2020). More generally, gamma oscillations have been proposed as a biomarker of mood disorder (Herrmann and Demiralp, 2005; Fitzgerald and Watson, 2018) and investigated as a potential biomarker of ketamine antidepressant effect efficacy. Recently, one study from Nugent and colleagues reported that higher post-ketamine gamma power in 35 nonmedicated MDD patients was associated with better response in subjects with lower baseline gamma (Nugent *et*

al., 2019). Historically, gamma amplitudes have been considered too vulnerable to contamination and noise to be evaluated and have often been overlooked in the literature, although new methods for dealing with the noise are now available (Nottage and Horder, 2016). The possibility of capturing gamma modulation from the home via portable wireless devices is a critical finding which opens new possibilities in psychiatric clinical research and more specifically in mood related disorders.

Contrary to our initial hypothesis, no alpha power differences were captured during the infusion despite it being a well-described and replicated result from the literature (Bojak, Day and Liley, 2013; de la Salle *et al.*, 2016; Vlisides *et al.*, 2018). Vlisides and colleagues who used the same dosing protocol in a similar young and healthy population, reported alpha band power decrease of ~1dB when looking at parietal regions, although we note differences in the baseline approach used (Vlisides *et al.*, 2018). This decrease seems relatively small compared to the resolution of our PSDs. They also examined a later time-window during the course of the infusion (between 26-37 min after the infusion start) compared to our analyses which were focused on the 10 to 20 min time-window after the infusion start. One explanation could be that ketamine blood concentration was still too small at that time to lead to significant disruptions. Our plasma analyses confirmed that the ketamine concentration was building over time and maximal 40 mins after the beginning of the infusion. Future analyses should consider looking at a later time-window. Additionally, Vlisides and colleagues also administered patients with a nausea prophylaxis (ondanstron, 8 mg i.v.) which may have affected the EEG recordings. Despite the lack of significance in my results, I nonetheless note that the F-values seem to follow an inverted U-shape curve peaking around 11hz during the infusion which could represent a trend toward significance.

None of the ERP analyses revealed significant modulations by the drug immediately around the ketamine infusion which refuted my hypotheses. I also did not observe any effects in the at-home dataset. As previously stated, a possible explanation for the in-laboratory results is that the effect

sizes targeted were too small. The fact that for all ERP eliciting tasks, we were able to observe the targeted ERPs of interest informs us that this lack of significance is not related to a problem with tasks or ERP elicitation per se. This suggest that the in-laboratory analyses conducted in this chapter utilizing single-session time point around the infusion may have been underpowered. Future studies should consider increasing the numbers of trials captured per block and/or make use of robust aggregating methods or regression models to clean further the data and increase detection thresholds (Smith and Kutas, 2015). An alternative explanation for the lack of significant ERP modulation could also be that the ketamine dose used here was not large enough to produce detectable effects. The 0.5mg/kg dose was chosen as it is the currently recommended therapeutical dose for the treatment of depressive symptoms (Sanacora *et al.*, 2017). However, quite a few studies reporting ERP impairments used a bolus and/or higher doses of ketamine up to 0.9mg/kg (Schwertner *et al.*, 2018). Additionally, some used S-ketamine, a more potent enantiomer compared to racemic ketamine (Schwertner *et al.*, 2018). While ERPs in-laboratory analyses may have been under-powered to detect any drug effects, at-home analyses made use of 3-session aggregates which should have been sufficient to capture an effect. To the best of my knowledge, this is the first time according that repeated ERP paradigms were administered to a cohort of healthy volunteers during the week after an administration of ketamine. Thus, it is very plausible that the effects of ketamine on brain and cognitive functions were short-lived and did not persist in the week after the ketamine administration.

6.2.3 Gamification of cognitive task

Analyses of brain data recorded in *Empirical Chapter 3* suggest that the Non-Target trials of the gamified Oddball task may have recruited cognitive functions different or additional to those it was designed to target. Specifically, the frontocentral distribution of the Non-Target P300, and its greater amplitude, compared to the Target P300 are surprising findings. In the literature, Non-Target signals are typically reported to be maximal in centroparietal regions and of smaller amplitude compared to Target P300 (Polich, 2007). Frontocentral distributions are commonly

associated with *Nogo* P300 (Salisbury *et al.*, 2004; Smith, Johnstone and Barry, 2006; Albert *et al.*, 2013). The Nogo P300 is typically elicited in Go/Nogo task that emphasizes the cognitive demand on infrequent Nogo trials (Albert *et al.*, 2013). When Nogo trials are infrequent, subjects must deploy higher cognitive control to suppress the prepotent Go response (Pires *et al.*, 2014). A potential explanation for my observations could be that the gamification process introduced inhibition-task-like features in Astrotap. In traditional Oddball tasks, Non-Target stimuli are task-irrelevant and can be ignored. In Astrotap's conceptual framework, players are penalized when incorrectly hitting the Non-target stimulus by receiving a score punishment (i.e., point deduction) as well as a buzzing sound corresponding to a negative feedback. Consequently, these stimuli may no longer be passively ignored but rather actively avoided. Additionally, stimulus locations are highlighted prior to stimulus presentation so that participants' gaze will be orientated to where the stimulus appears (i.e., functionally similar to a fixation cross). This may have primed participants and effectively resulted in an undesired warning cue, a feature also typically found in inhibition tasks (Smith, Johnstone and Barry, 2006). Finally, shorter reaction times for Target stimulus were also rewarded with more points, prompting participants to always stay ready to respond in case of the appearance of a Target stimulus. This may have resulted in effortful inhibition when Non-Target trials were presented, leading eventually to the generation of an inhibitory P300 in place of the small positive deflection typically observed in standard trials. As described by Smith et al., 2006: *"Where [the] response preparation is inappropriate, inhibition is necessary, and presumably greater inhibition is required following greater response preparation."* (Smith, Johnstone and Barry, 2006). This finding is critical as it highlights a potential consequence of gamification which is a shift of brain systems and functions engaged. It is not surprising that gamification may lead to the simultaneous recruitment of multiple cognitive functions as it is meant to be more ecologically valid. In the real world, cognitive functions rarely function in isolation. Nonetheless, it is critical for the researchers to be aware of this phenomenon when contextualising the findings.

Unexpected topographies were also observed in two participants during Target trials. In each case, a bilateral pattern could be observed around 300ms post stimulus presentation. A possible explanation could be that this pattern relates to the use of response buttons located on either side of the screen during the task. This may have led to lateralised motor artefacts and/or motor related brain activity. This bilateral pattern may correspond to the mu rhythm. The mu rhythm or activity is primarily 8–13 Hz and is thought to be linked to the observation or the execution of motor activity. It is typically observed on the posterior side of the sensorimotor cortex and on the contralateral side of the motor movement (Saltuklaroglu *et al.*, 2018; Inamoto *et al.*, 2023). Participants may not have always used the same hand or could have used both hands to answer the target stimulus and this could have led to unexpected bilateral patterns. The appearance of this patterns in only two participants limited our opportunities to study further this phenomenon. However, future work could evaluate this hypothesis by systematically manipulating response button directionality/usage. Spectrograms could be used to see if any clear mu activity can be isolated, and participants' behaviour could be analysed in parallel to see if the response buttons are used consistently within and across gameplays.

Analyses of behavioural and self-reported data from *Empirical Chapter 1* and *Empirical Chapter 3* revealed some heterogeneity in participant game and task strategies. Furthermore, *Empirical Chapter 1* suggested that older adults preferred to use slower and more accurate strategy over speed which replicates previous reports from the literature (Ghisletta *et al.*, 2018). In *Empirical Chapter 3*, I observed a variety of game strategies with people sometimes favouring either speed or accuracy, or neither of them. Some participants reported focusing more on targeting aliens while others focused on avoiding astronauts. One person also reported changing strategy during the course of the study. It should be noted that one of the participants who reported favouring speed and accuracy equally also mentioned attempting to shoot the aliens as fast as possible to get more points which led them to shoot a few astronauts in the process. This seems to be in contradiction and incompatible with the balanced speed-accuracy trade-off strategy reported and

could suggest that the feedback questionnaire may not have accurately captured participant's strategy. When evaluating if participants' strategies could relate to the Non-Target ERP topographies, no clear trend was observed. That is, regardless of what the participants reported, all Non-Target ERP exhibited a frontocentral distribution which is traditionally associated with inhibition processes. These observations suggest that complex mechanisms may have been at play when participants devised their strategy. The lack of consistency in the participants' feedback and of agreement between the inhibitory signals observed in the EEG and the feedback questionnaires may be explained by a few factors. First and as mentioned above, it may be that the feedback questionnaires did not accurately capture the participants' experiences. Second, it could be that participants did not properly recall their strategies and/or had not enough self-awareness to report it correctly.

In laboratory settings, participant strategies are usually well controlled by the experimenters who regularly check if the participants are doing the tasks as instructed and correct them if required. Moreover, automated checks implemented directly within the tasks prompt participants to be faster or more accurate (depending on the cognitive functions evaluated and the task) if their performance reveals that they do not adhere to the task instructions. When participants complete recordings from the home, the experimenter can lack insight on a participant's strategy. My analyses revealed that, even in a small sample, the strategies employed were heterogenous. These results suggest that it could be interesting in future iterations of the technology to add automated features to ensure a better adherence to instructions. For example, a quiz at the end of the instruction to ask them if they understood the guidelines well could be implemented. Another idea could be to reveal text prompts during the task relating to participants behavioural performance if they are too slow or not following the tasks instructions. Although an unexpected result, these different choices and/or changes in strategy may be interesting phenomena to investigate when evaluating cognitive functions. Future analyses could attempt to identify if specific strategies are characterized by distinct ERPs.

Finally, the general decrease of the Non-Target P300 signal amplitudes across sessions in some participants was a novel finding. Few studies have looked at the effects of repeated P300 task administration and the reported results are mixed. Source estimation analyses computed by Hartmann and colleagues revealed that repeated administrations of a Go/Nogo task yielded significant Stimulus-by-Session interaction reflecting an amplitude decrease in inferior frontal cortices for Nogo trials after 12 blocks of 60 trials (Hartmann, Sallard and Spierer, 2016). Repeated administration of an auditory Oddball button press task within the context of a caffeine challenge reported a lack of effects of block on P300 amplitudes both in the placebo and caffeine conditions after completing 6 consecutive blocks of ~20 trials (Pan, Takeshita and Morimoto, 2000). Benikos and colleagues evaluated the effect of training on different levels of difficulty in Go/Nogo tasks and reported a training-induced augmentation in the Nogo P300 in the hardest condition after 8 blocks of 100 trials each (Benikos, Johnstone and Roodenrys, 2013). Finally, another study reported no differences in P300 amplitude in a Go/Nogo task in both conditions after completing one session per day for 6 consecutive days, each session consisting of 2 blocks of 200 trials (Jodo and Inoue, 1990). The reason of the observed decrease in amplitude in the Non-Target trials remains unclear. One hypothesis could be that as participants get familiar with the game, the cognitive load decreases with sessions, which in turns decrease the signal amplitudes.

6.3 Limitations

Empirical Chapter 1 included some limitations. The ideal comparison between dry vs. wet EEG would involve near-daily at-home wet EEG, but the burden of this design renders this unfeasible as wet EEG requires the presence of a trained technician for set-up. There are several likely sources of data variability. Some brain data variability could be related to task learning effects rather than device performance. In addition, it is also likely that participants improved at using the platform during the first week of recordings. To quantify the amount of variability emerging from learning how to use the headset itself, future studies should consider first providing participants with the tablet before introducing the headset at a later stage. The headset's correct

placement when the participant was in the home was not controlled and may have introduced noise in the signals. However, the risk of misplacement was mitigated using a semi-rigid neoprene frame which ensured correct relative electrodes positions. The headset has also natural orientation points to ensure a consistent correct positioning: the earpieces go behind the ears and the front strap aligns with the brows. Specific emphasis was also given to participants during onboarding on the importance of headset placement and reminders were sent at the beginning of each session via the mobile app on the procedure to ensure a correct use. However, future studies may consider evaluating this specific question by taking pictures of participants in the home. Part of the signal variability may also originate from day-to-day changes related to lifestyle factors, mood, and stress levels, which I did not quantify here – and which this approach gives a unique opportunity to investigate in the future. Aggregating over days and weeks may have been confounded with processes fluctuating over time (e.g., cognitive decline or training effects). However, several factors suggest that sessions are largely fungible. Specifically, both reaction times and the number of trials rejected were stable across the two studies suggesting few training effects related to the learning of the task materials or the set-up of the dry EEG headset. Participants were neurotypical and no decline over time was expected in the relatively short span of my study. Finally, no increase in SME was observed as more data were aggregated.

Different preprocessing pipelines were applied to the dry data and the wet reference dataset, and it is possible that further optimization of data exclusion strategies could result in improved SME levels for the wet laboratory and/or dry home data. It should also be noted that as the data quality analyses conducted consisted in post-hoc analyses of datasets collected for other purposes, the two study protocols were substantially different. However, the onboarding procedure as well as the tasks used on both studies were the same. I led the training of the research assistants involved in the two studies and participated in the data collection in both studies. That way, I ensured that the onboarding procedure were the same for both studies.

Another limitation of this study was the limited subjective feedback collected from the participants, that is only at a single timepoint at the very end of these studies. Future studies should consider adding additional measure of the SUS at various timepoints throughout the study protocol to evaluate if the participants' attitude and opinions toward the technology changed as they got more familiar with the platform. Adding measurement at the beginning of the study before and after being trained on how to use the technology could also inform how the participant feel about the platform before engaging with it and reveal how the training modulates their subjective feelings.

Empirical Chapter 1 was also limited in that the younger cohort dataset did not include any females, preventing us from evaluating the impact of the interaction between age and sex on the variability of the data. Additionally, future studies will have to test validity in specific target clinical populations for whom it may be relevant to increase stimulus size and presentation time. Finally, the studies differed on numerous levels including site, age, sex, educational background, motivation for participation, task protocol, cadence of sessions, and number of in-laboratory sessions, which prevented us from performing a direct comparison.

Empirical Chapter 2 also had several limitations. At the time when the study and hypotheses were designed, few studies had been conducted using EEG to analyses ketamine effects. More recent research revealed additional EEG metrics of interest to be considered within the context of a ketamine intervention. Specifically, future studies should consider including alpha asymmetry, and delta and theta band activities in the analyses as they seem to be modulated by ketamine in MDD patients (De la Salle 2022). Initial ketamine studies have primarily focused on the alpha frequency band as one of the main symptoms reported by patients was a decrease in overall arousal and vigilance. However more recent studies have reported modulation of lower frequency bands which may have been detectable in our analyses (see Figure 43). Future analyses should consider testing across a larger range of frequencies. Next, our study did not include any patient population. This prevented us from computing any responder vs. non-responders' analyses. It is

expected that one of the strengths of remote EEG over traditional study design will be the ability to generate more robust individual baselines which may help us to stratify our participants to optimize drug response and/or the isolation of a drug effect. For this reason, studies in patients may be more informative of the underpinnings of ketamine action on brain activity as they make it possible to quantify drug effect on a clinical endpoint (e.g., in this case depressive symptoms). Finally, no female participants were included in this study which prevented us looking at sex-specific differences. A former study by Colic and colleagues reported female-specific modulation of protein regulating the cytoskeleton activity and synaptic plasticity (Colic *et al.*, 2019). Including female participants in future studies could increase the effect size of the signals I attempted to detect here.

Finally, *Empirical Chapter 3* also included several limitations. First, the number of participants included was too small to perform quantitative analyses. It also prevented us from comparing this dataset to the ones of Empirical Chapter 1. Indeed, as the sample sizes were greatly different (between 6 to 7 times larger), conclusions around signal variability would have been quite limited**.** The number of excluded participants was quite high (e.g., 40%) and may indicate issues with the training of the research assistants who were new to the administration of wet EEG recordings. This may have resulted in an especially noisy dataset. Second, it would have been beneficial to include a standard non-gamified traditional Oddball to disentangle individual differences from gamification effect. Future studies should consider including a reference traditional paradigm to address this point. Indeed, it may be that the Target P300 of some participants was attenuated by motor-related activity or artefacts, resulting in lower Target P300 compared to Non-target P300. Data collection for this chapter was limited due to time constraints related to the Covid-19 pandemic. Because of this, only 10 subjects were recruited in this study and recording were limited to gamified task only as including another task in the study would have obliged us to ask participants to come back in the laboratory for a third testing session. Another limitation of this study was that the questionnaire around participants' strategies was only sent a month after data

collection. This is due to the fact that the research team only belatedly thought of soliciting a subjective post-hoc report. It is possible that because of the delays between the questionnaires and the testing sessions, participants may not have recalled well the details of their strategy. Finally, a larger number of participants would have allowed us to perform source localisation analyses which could have been informative on the neural generators and the nature of the signals observed.

To finish, another limitation of this thesis was the lack of visibility on some of the parameters used in the gamified tasks that may have had an important role in the ERP elicitations. Indeed, Cumulus Neuroscience declined to disclose some of the stimulus features considered commercially sensitive. This prevented me from analysing and commenting on whether the task parameter choices could have played a role in the unexpected results observed in the gamified oddball task. It also prevented me from evaluating, in all tasks, how these parameters compared to the ones traditionally using within the field. It is a common knowledge in the field that the way the stimuli are presented impacts the generation and the characteristics of the ERPs. This information would have provided critical insights to contextualise the results presented in this thesis.

6.4 Relevance for future directions

In 2016, neurological disorders were the leading cause of disability and the second leading cause of death worldwide (Feigin *et al.*, 2019), while 16% of the world population was affected by a mental or addictive disorder (Rehm and Shield, 2019). When looking at neurodegenerative disorder, AD and other dementias ranked 7th in the top 10 global causes of death in 2019 (WHO, Global health Estimates). One of the key problems impeding the progression of fundamental brain research and its translation into clinically relevant interventions is the lack of objective and reliable disease biomarkers (Kirkpatrick *et al.*, 2021). Historically, both in psychiatric and neurodegenerative research, diagnosis and disease progression is assessed primarily by means of clinical judgement, based on examinations and patients' report only completed a few times a year. This approach is problematic as diagnoses are subject to clinician's bias and patients' lifestyle-

related variability in brain activity and behaviours when they visit the clinics. Additionally, patients' reports are also subject to recall bias (e.g., remembering particularly salient, and/or more recent events). The weak validity and reliability of psychiatric diagnosis is not a novel issue (Owen, 2014). Publications on the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 have reported intraclass κ-coefficients of reliability qualified as questionable and unacceptable for at least 5 disorders including depressive and anxiety disorders (Vanheule *et al.*, 2014). The lack of objective disease monitoring tools negatively impacts patients who can experience extreme delays before receiving a diagnosis or may even get misdiagnosed. Patients suffering from bipolar I disorder typically wait from 3.5 to 6.5 years on average before the confirmation of their diagnosis and over 40 % of patients suffering from Frontotemporal Degeneration have reported being originally misdiagnosed with another condition (Cha *et al.*, 2009; Lublóy *et al.*, 2020; Dacks *et al.*, 2021).

The Biomarker Definitions Working Group proposed to define biomarkers as a ''*characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*'' (Atkinson *et al.*, 2001). While diagnosis procedures would hugely benefit from being grounded in quantifiable biological variables, the development of biomarkers in brain research is predicted to have a multi-level impact on how mental and neurological disorders are studied and treated. Indeed, reliable and valid biomarkers hold the promise of predicting and monitoring patient treatment response, accelerating clinical trials, and boosting fundamental research by allowing a better stratification of populations (Linden, 2012). Kirkpatrick et al. comprehensively summarized the challenges associated with the identification of reliable biomarkers in psychiatry (Kirkpatrick *et al.*, 2021). A large proportion of these challenges relate to the fluctuating nature of brain disorders as well as their lack of specific symptoms. Symptoms are the results of the combination of several brain networks as opposed to isolated regions. Key between-group differences seem to lie in the relative activation of different brain regions (Linden, 2012). Symptoms also fluctuate with time and are unspecific and overlap between conditions, which lead to diagnosis instability. For instance,

psychotic episodes may be experienced by patients suffering from BD, Schizophrenia, MDD or can be triggered by substance abuse. A potential solution to refine disease characterization is to increase the sampling rate and time window during which brain and behavioural data are captured. However, increased data collection comes with a cost and require rigorous protocol standardization to be meaningful (Kirkpatrick *et al.*, 2021).

In the context of neurodegenerative research, the dry EEG approach described here could be especially useful for prodromal phase studies as change can emerge over years (Calabrò *et al.*, 2021). One could imagine asking an at-risk population to complete 2 weeks of recordings every year to detect subtle changes in brain function and cognition. According to the Alzheimer's Disease international association, 55 million people lived with dementia during 2020 and this number is estimated to reach 139 million in 2050. There is still currently no curative treatment for AD type of dementia and new avenues of research are definitively needed. A growing body of evidence shows that EEG is sensitive to cognitive decline, at least. In the context of clinical trials of new therapies, recording across a week prior to a therapeutic intervention could establish a baseline of brain activity more robust to daily fluctuations (e.g., caused by lifestyle factors). Once identified, changes in baseline metrics over time could act as biomarkers for the detection and monitoring of neurodevelopmental, neuropsychiatric, or neurodegenerative disorders (Levine *et al.*, 2015; Ausó, Gómez-Vicente and Esquiva, 2020; Kirkpatrick *et al.*, 2021; Mofrad *et al.*, 2021). Brain changes associated with neurodegenerative disorders typically occur over years (Cassani *et al.*, 2018; Calabrò *et al.*, 2021), while neurodevelopmental disorders impact brain function across the lifespan (Boivin *et al.*, 2015; Thapar, Cooper and Rutter, 2017). Conversely, some disorders (e.g., Multiple Sclerosis, Lewy Body Dementia, Schizophrenia) are also characterized by fluctuating cognitive symptoms at the scale of days or week (McKeith *et al.*, 1996; Pillmann *et al.*, 2002; Pillmann and Marneros, 2003; Benedict *et al.*, 2014; Powell *et al.*, 2017; Matar *et al.*, 2020). Consequently, cognitive biomarkers are likely to be more effective when brain activity is

intermittently monitored over long periods (Lau-Zhu, Lau and McLoughlin, 2019), or in intensive bursts of frequent sampling (Campbell *et al.*, 2020).

Resting state EEG (rsEEG) may be particularly useful as a scalable method because the participant does not have to engage in a specific task, yet rsEEG appears sensitive to cognitive decline over time, albeit in groups with mild symptoms at baseline (cf. prospectively in a healthy cohort). For example, 54 MCI, 50 mild AD, and 45 cognitively unimpaired (CU) older adults each had their EEG recorded 1-year apart (Babiloni *et al.*, 2014). At baseline, alpha-band power was lowest in the mild AD group, highest in the CU group, whereas the MCI group had intermediate values. At follow-up, the MCI group's alpha power was further decreased, suggesting that rsEEG could be sensitive to disease progression. A review of results from 14 studies that applied machine learning to rsEEG data reported classification accuracies between CU and MCI patients between 77–98%, sensitivity between 75–100% and specificity between 75–97% (Rodrigues *et al.*, 2021). A study with a large sample (n = 496) healthy older adults reported that resting-state prefrontal biomarkers could predict global cognition (Mini-Mental State Examination score) with moderate accuracy (maximum intraclass correlation = 0.76) (Choi *et al.*, 2019).

The P300 ERP is also particularly promising for detecting cognitive decline. Both the P300 amplitude and latency have been shown to be cognitively relevant in the research literature (Horvath *et al.*, 2018; Babiloni *et al.*, 2020). In particular, the P300 amplitude decline in older age (Dinteren *et al.*, 2014), and is considered to be a marker of Alzheimer's disease pathology (Horvath *et al.*, 2018; Babiloni *et al.*, 2020). P300 latency correlates with degree of cognitive deficit in AD (Cintra *et al.*, 2018; Horvath *et al.*, 2018; Fruehwirt *et al.*, 2019; Porcaro *et al.*, 2019; Babiloni *et al.*, 2020); and is increased in AD compared to MCI, and MCI patients in turn have longer latencies than age-matched controls (Horvath *et al.*, 2018; Babiloni *et al.*, 2020). The P300 latency is correlated with cognitive impairment, as measured by the Mini-Mental State Exam (Lee *et al.*, 2013) and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (Bonanni *et al.*, 2010). Finally, using EEG phase-amplitude coupling measures extracted from an Oddball task, Dimitriadis

and colleagues demonstrated it was possible to distinguish 15 cognitively impaired older adults from 25 MCI with an accuracy of 95%, a sensitivity of 96%, and a specificity of 93% (Dimitriadis *et al.*, 2015).

7 Conclusion

This thesis has contributed to the field in the following ways. I evaluated two innovative neurocognitive studies with repeated sampling of brain data in a remote setting, conducted with cohorts of younger and older age profiles. The dry EEG platform was easily deployable in the field; participants found it quite usable and repeatedly engaged with the technology while in the home. The recorded behavioural and ERP data were comparable to traditional wet EEG paradigms. This generated rich longitudinal data that would not have been possible in a traditional experimental laboratory-based design. Due to the volume of data collected (i.e., near daily), multiple strategies were employed to improve signal quality, including aggregation of multiple sessions within subjects and conservative data inclusion protocols. ERP data were similar in morphology to those reported in the literature from laboratory-based studies. Data quality matched what is observed in wet EEG after data aggregation. The use-case pharmacological trial demonstrated that it is possible to successfully deploy the technology in the context of a drug study that included intensive burst of recordings occurring alternatively in the home or the laboratory. Results only partially emulated the wet EEG literature but other important factors including the timing of the recordings and drug dosage have most likely contributed to the lack of significance observed. The in-depth analysis of a gamified task brought key insights to the field on how adding game-like features may impact the cognitive functions recruited during a cognitive task. It also enabled the identification of promising avenues for the improvement of the gamification process in future iteration of the technology.

Overall, this thesis demonstrated that remote dry EEG is a suitable tool for cognitive neuroscience investigations, and has the potential to provide objective, frequent and patient-centred tracking of biomarkers of functional neurophysiology. This approach has potential to facilitate large scale

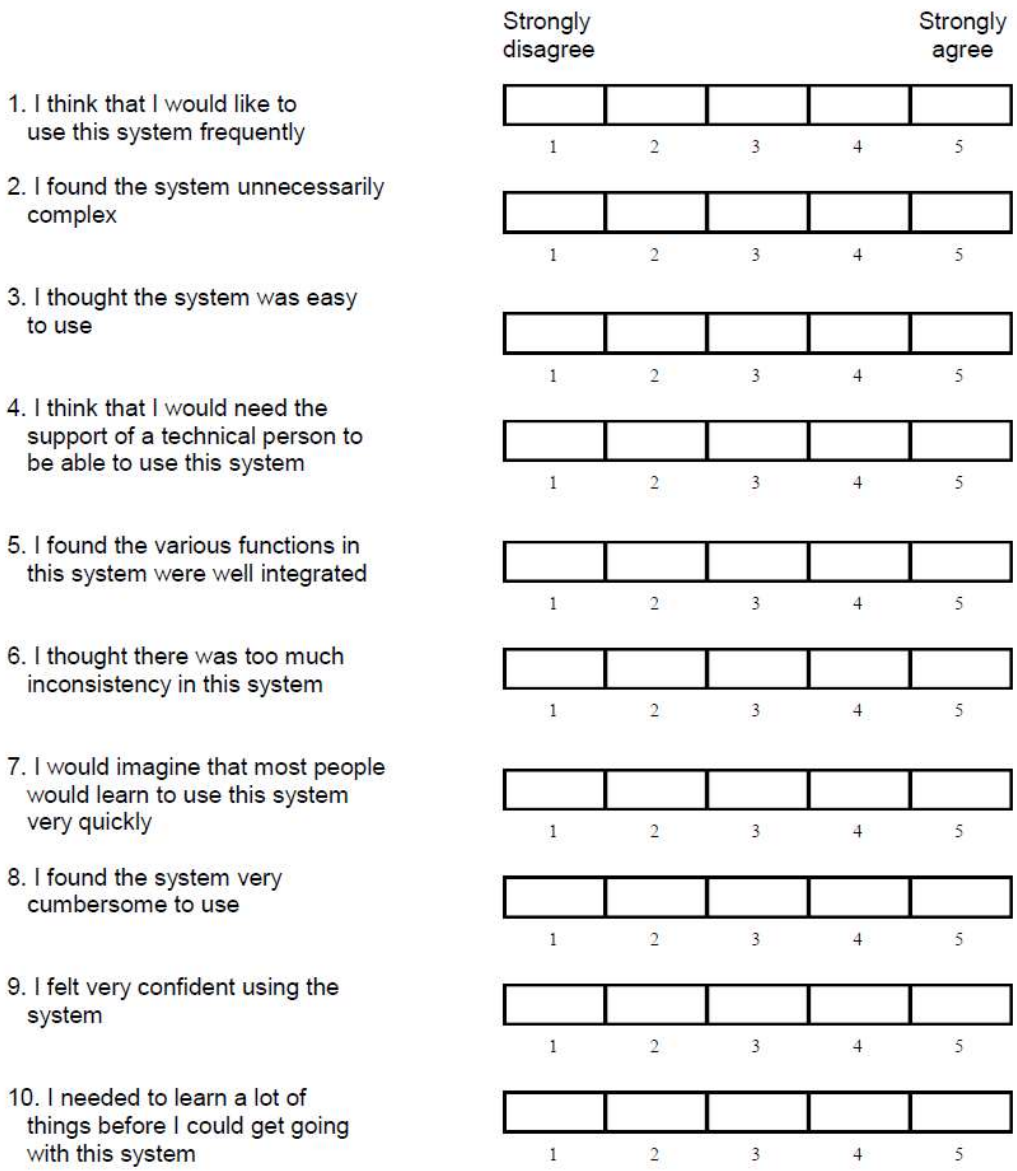
longitudinal studies of neurodegenerative, neurodevelopmental, and neuropsychiatric disorders that manifest on different time scales.

8 Appendix

8.1 System Usability Scale

System Usability Scale

© Digital Equipment Corporation, 1986.



Supplementary Figure 1: System Usability Scale extracted from (J. Brooke, 1996)

8.1.1 Instruction and scoring of the System Usability Scale

Instructions on how to score the System Usability Scale are provided in the original publication by Brook (Brooke, 1996). Please see below the original scoring instructions:

"SUS yields a single number representing a composite measure of the overall usability of the system being studied. Note that scores for individual items are not meaningful on their own. To calculate the SUS score, first sum the score contributions from each item. Each item's score contribution will range from 0 to 4. For items 1,3,5,7, and 9 the score contribution is the scale position minus 1. For items 2,4,6,8 and 10, the contribution is 5 minus the scale position. Multiply the sum of the scores by 2.5 to obtain the overall value of SU.

SUS scores have a range of 0 to 100."

8.2 Empirical chapter 2 : Ketamine metabolites analyses

Plasma concentration of ketamine, norketamine and hydroxy-norketamine were analysed 20 mins and 40 mins after the beginning of the infusions. Study samples were analysed as one or more batches using the qualified LC-MS/MS methods. Plasma standards and samples were extracted by the addition of organic solvent, containing the internal standards, for protein precipitation. A sample batch consisted of the following: 3 replicates of a system suitability standard (containing the analyte and internal standard), calibration standards in ascending order including a blank sample (without internal standard), a zero sample (with internal standard), and at least 6 non-zero standards and the study samples followed by the 3 replicates of the system suitability sample. Calibration standards bracketed an analysis batch of greater than 40 samples. The analysis batch was considered acceptable if the acceptance criteria stated hereafter were met. Samples determined to be above the highest level of quantitation (AQL) were acceptable up to 20% above the highest calibration standard. AQL samples which did not meet these criteria were diluted and

re-assayed along with a corresponding dilution quality control standard. Dilution standards were acceptable if they were within 20% accuracy of the target concentration.

The requirements for acceptance of the methods were:

1. at least 75% of the non-zero calibration standards must be included in the calibration curve with all back-calculated concentrations within ± 20% nominal concentrations (except for the lower level of quantification, LLOQ, where ± 25% is acceptable),
2. the correlation coefficient (r) of the calibration curve must be greater than or equal to 0.99, the area ratio variation between the pre- and post-run injections of the system suitability samples is within ± 25%.

9 References

Aarts, A. A. *et al.* (2015) 'Estimating the reproducibility of psychological science', *Science*, 349(6251), pp. aac4716–aac4716. doi: 10.1126/science.aac4716.

Abdallah, C. G. *et al.* (2015) 'Ketamine and rapid-acting antidepressants: A window into a new neurobiology for mood disorder therapeutics', *Annual Review of Medicine*, 66, pp. 509–523. doi: 10.1146/annurev-med-053013-062946.

Abiri, R. *et al.* (2020) 'A Usability Study of Low-Cost Wireless Brain-Computer Interface for Cursor Control Using Online Linear Model', *IEEE Transactions on Human-Machine Systems*, 50(4), pp. 287–297. doi: 10.1109/THMS.2020.2983848.

Adinda, P. P. and Suzianti, A. (2018) 'Redesign of user interface for E-government application using usability testing method', *ACM International Conference Proceeding Series*, pp. 145–149. doi: 10.1145/3290420.3290433.

Afridi, S. K. *et al.* (2013) 'A randomized controlled trial of intranasal ketamine in migraine with prolonged aura', *Neurology*, 80(7), pp. 642–647. doi: 10.1212/WNL.0b013e3182824e66.

Ahnaou, A. *et al.* (2017) 'Ketamine: differential neurophysiological dynamics in functional networks in the rat brain', *Translational Psychiatry*, 7(9), p. e1237. doi: 10.1038/TP.2017.198.

Al-Taleb, M. K. H. *et al.* (2019) 'Home used, patient self-managed, brain-computer interface for the management of central neuropathic pain post spinal cord injury: Usability study', *Journal of NeuroEngineering and Rehabilitation*, 16(1), p. 128. doi: 10.1186/s12984-019-0588-7.

Alain, C. *et al.* (2002) 'Neurophysiological evidence of error-monitoring deficits in patients with schizophrenia', *Cerebral Cortex*, 12(8), pp. 840–846. doi: 10.1093/cercor/12.8.840.

Albert, J. *et al.* (2013) 'Spatiotemporal characterization of response inhibition', *NeuroImage*, 76,

pp. 272–281. doi: 10.1016/j.neuroimage.2013.03.011.

AlGhannam, B. A. *et al.* (2018) 'Towards a Standard Arabic System Usability Scale: Psychometric Evaluation using Communication Disorder App', *International Journal of Human-Computer Interaction*, 34(9), pp. 799–804. doi: 10.1080/10447318.2017.1388099.

Arnal, P. J. *et al.* (2020) 'The dreem headband compared to polysomnography for electroencephalographic signal acquisition and sleep staging', *Sleep*, 43(11). doi: 10.1093/sleep/zsaa097.

Assenza, G. and Lazzaro, V. Di (2015) 'A useful electroencephalography (EEG) marker of brain plasticity: delta waves', *Neural Regeneration Research*, 10(8), p. 1216. doi: 10.4103/1673-5374.162698.

Atkinson, A. J. *et al.* (2001) 'Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework', *Clinical Pharmacology and Therapeutics*, 69(3), pp. 89–95. doi: 10.1067/mcp.2001.113989.

Ausó, E., Gómez-Vicente, V. and Esquiva, G. (2020) 'Biomarkers for alzheimer's disease early diagnosis', *Journal of Personalized Medicine*, 10(3), pp. 1–27. doi: 10.3390/jpm10030114.

Babiloni, C. *et al.* (2014) 'Cortical sources of resting state electroencephalographic alpha rhythms deteriorate across time in subjects with amnesic mild cognitive impairment', *Neurobiology of Aging*, 35(1), pp. 130–142. doi: 10.1016/j.neurobiolaging.2013.06.019.

Babiloni, C. *et al.* (2020) 'What electrophysiology tells us about Alzheimer's disease: a window into the synchronization and connectivity of brain neurons', *Neurobiology of Aging*, 85, pp. 58–73. doi: 10.1016/j.neurobiolaging.2019.09.008.

Badcock, N. A. *et al.* (2013) 'Validation of the Emotiv EPOC® EEG gaming systemfor measuring research quality auditory ERPs', *PeerJ*, 2013(1). doi: 10.7717/peerj.38.

Bagby, R. M., Taylor, G. J. and Parker, J. D. A. (1994) 'The twenty-item Toronto Alexithymia scale-

II. Convergent, discriminant, and concurrent validity', *Journal of Psychosomatic Research*, 38(1), pp. 33–40. doi: 10.1016/0022-3999(94)90006-X.

Baker, M. (2015) 'Over half of psychology studies fail reproducibility test', *Nature*. doi: 10.1038/nature.2015.18248.

Baker, T. E. and Holroyd, C. B. (2011) 'Dissociated roles of the anterior cingulate cortex in reward and conflict processing as revealed by the feedback error-related negativity and N200', *Biological Psychology*, 87(1), pp. 25–34. doi: 10.1016/j.biopsycho.2011.01.010.

Bangor, A., Kortum, P. T. and Miller, J. T. (2008) 'An empirical evaluation of the system usability scale', *International Journal of Human-Computer Interaction*, 24(6), pp. 574–594. doi: 10.1080/10447310802205776.

Barbanoj, M. J. *et al.* (2006) 'Quantifying drug-drug interactions in pharmaco-EEG', *Clinical EEG and Neuroscience*. SAGE Publications Inc., pp. 108–120. doi: 10.1177/155005940603700208.

Barber, T. X. and Silver, M. J. (1968) 'Fact, fiction, and the experimenter bias effect', *Psychological Bulletin*, 70(6 PART 2), pp. 1–29. doi: 10.1037/h0026724.

Barbey, F. *et al.* (2022) 'Neuroscience from the comfort of your home: Repeated, self-administered wireless dry EEG measures brain function with high fidelity', *Frontiers in Digital Health*, 4(944753). doi: 10.3389/fdgth.2022.944753.

Bares, M. *et al.* (2017) 'The Comparison of Effectiveness of Various Potential Predictors of Response to Treatment with SSRIs in Patients with Depressive Disorder', *Journal of Nervous and Mental Disease*, 205(8), pp. 618–626. doi: 10.1097/NMD.0000000000000574.

Barham, M. P. *et al.* (2017) 'Acquiring research-grade ERPs on a shoestring budget: A comparison of a modified Emotiv and commercial SynAmps EEG system', *Psychophysiology*, 54(9), pp. 1393–1404. doi: 10.1111/psyp.12888.

Barry, R. J. *et al.* (2005) 'Caffeine effects on resting-state arousal', *Clinical Neurophysiology*,

116(11), pp. 2693–2700. doi: 10.1016/j.clinph.2005.08.008.

Barry, R. J., Steiner, G. Z. and De Blasio, F. M. (2016) 'Reinstating the Novelty P3', *Scientific Reports*, 6(1), p. 31200. doi: 10.1038/srep31200.

Başar, E. (2013) 'A review of gamma oscillations in healthy subjects and in cognitive impairment', *International Journal of Psychophysiology*, 90(2), pp. 99–117. doi: 10.1016/j.ijpsycho.2013.07.005.

Bateson, A. D. *et al.* (2017) 'Categorisation of Mobile EEG: A Researcher's Perspective', *BioMed Research International*, 2017. doi: 10.1155/2017/5496196.

Benedict, R. H. B. *et al.* (2014) 'Characterizing cognitive function during relapse in multiple sclerosis', *Multiple Sclerosis Journal*, 20(13), pp. 1745–1752. doi: 10.1177/1352458514533229.

Benikos, N., Johnstone, S. J. and Roodenrys, S. J. (2013) 'Varying task difficulty in the Go/Nogo task: The effects of inhibitory control, arousal, and perceived effort on ERP components', *International Journal of Psychophysiology*, 87(3), pp. 262–272. doi: 10.1016/j.ijpsycho.2012.08.005.

Berke, L., Huenerfauth, M. and Patel, K. (2019) 'Design and psychometric evaluation of American sign language translations of usability questionnaires', *ACM Transactions on Accessible Computing*, 12(2). doi: 10.1145/3314205.

Berron, D. *et al.* (2022) 'Feasibility of Digital Memory Assessments in an Unsupervised and Remote Study Setting', *Frontiers in Digital Health*, 4, p. 75. doi: 10.3389/fdgth.2022.892997.

Beul-Leusmann, S. *et al.* (2014) 'Usability evaluation of mobile passenger information systems', *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 8517 LNCS(PART 1), pp. 217–228. doi: 10.1007/978-3-319-07668-3_22.

Bianchi, M. and Baulieu, E. E. (2012) '3β-Methoxy-pregnenolone (MAP4343) as an innovative

therapeutic approach for depressive disorders', *Proceedings of the National Academy of Sciences of the United States of America*, 109(5), pp. 1713–1718. doi: 10.1073/pnas.1121485109.

Biondi, A. *et al.* (2021) 'Remote and long-term self-monitoring of electroencephalographic and noninvasive measurable variables at home in patients with epilepsy (EEG@HOME): Protocol for an observational study', *JMIR Research Protocols*, 10(3), p. e25309. doi: 10.2196/25309.

Bohannon, J. (2015) 'Many psychology papers fail replication test', *Science*, 349(6251), pp. 910–911. doi: 10.1126/science.349.6251.910.

Boivin, M. J. *et al.* (2015) 'Reducing neurodevelopmental disorders and disability through research and interventions', *Nature*. Nature Publishing Group, pp. S155–S160. doi: 10.1038/nature16029.

Bojak, I., Day, H. C. and Liley, D. T. J. (2013) 'Ketamine, propofol and the EEG: A neural field analysis of HCN1-mediated interactions', *Frontiers in Computational Neuroscience*, 7(MAR), p. 22. doi: 10.3389/fncom.2013.00022.

Bonanni, L. *et al.* (2010) 'Une nouvelle analyse de l'intérêt des PE cognitifs P300 pour le diagnostic de démence: formes précoces de démence à corps de Lewy et maladie d'Alzheimer', *Neurophysiologie Clinique*, 40(5–6), pp. 255–265. doi: 10.1016/j.neucli.2010.08.001.

Borkowska, A. and Jach, K. (2017) 'Pre-testing of Polish Translation of System Usability Scale (SUS)', *Advances in Intelligent Systems and Computing*, 521, pp. 143–153. doi: 10.1007/978-3-319-46583-8_12.

Bremner, J. D. *et al.* (1998) 'Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS)', *Journal of Traumatic Stress*, 11(1), pp. 125–136. doi: 10.1023/A:1024465317902.

Bright, P., Jaldow, E. and Kopelman, M. D. (2002) 'The National Adult Reading Test as a measure of premorbid intelligence: A comparison with estimates derived from demographic variables',

Journal of the International Neuropsychological Society, 8(6), pp. 847–854. doi: 10.1017/S1355617702860131.

Brooke (1996) 'SUS: A "quick and dirty" usability scale', in Jordan et al. (eds) *Usability Evaluation in Industry*, pp. 189–194.

Brooke, J. (1996) 'SUS—a quick and dirty usability scale. 1996', *Usability evaluation in industry*, 189(194), pp. 4–7.

Brose, A. *et al.* (2012) 'Daily variability in working memory is coupled with negative affect: The role of attention and motivation', *Emotion*, 12(3), pp. 605–617. doi: 10.1037/a0024436.

Brose, A., Lövdén, M. and Schmiedek, F. (2014) 'Daily fluctuations in positive affect positively co-vary with working memory performance', *Emotion*, 14(1), pp. 1–6. doi: 10.1037/a0035210.

Brown, H. R. *et al.* (2014) 'Crowdsourcing for cognitive science - The utility of smartphones', *PLoS ONE*, 9(7), p. e100662. doi: 10.1371/journal.pone.0100662.

Buckley, R. F. *et al.* (2017) 'Computerized Cognitive Testing for Use in Clinical Trials: A Comparison of the NIH Toolbox and Cogstate C3 Batteries', *The journal of prevention of Alzheimer's disease*, 4(1), pp. 3–11. doi: 10.14283/jpad.2017.1.

Buhrmester, M., Kwang, T. and Gosling, S. D. (2011) 'Amazon's mechanical Turk: A new source of inexpensive, yet high-quality, data?', *Perspectives on Psychological Science*, 6(1), pp. 3–5. doi: 10.1177/1745691610393980.

Burns, A. and Iliffe, S. (2009) 'Alzheimer's disease', *BMJ (Online)*, 338(7692), pp. 467–471. doi: 10.1136/bmj.b158.

Bush, G., Luu, P. and Posner, M. I. (2000) 'Cognitive and emotional influences in anterior cingulate cortex', *Trends in Cognitive Sciences*, 4(6), pp. 215–222. doi: 10.1016/S1364-6613(00)01483-2.

Buysse, D. J. *et al.* (1989) 'The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research', *Psychiatry Research*, 28(2), pp. 193–213. doi: 10.1016/0165-1781(89)90047-4.

Buzsáki, G. and Watson, B. O. (2012) 'Brain rhythms and neural syntax: Implications for efficient coding of cognitive content and neuropsychiatric disease', *Dialogues in Clinical Neuroscience*, 14(4), pp. 345–367. doi: 10.31887/dcns.2012.14.4/gbuzsaki.

Caddy, C. *et al.* (2014) 'Ketamine as the prototype glutamatergic antidepressant: Pharmacodynamic actions, and a systematic review and meta-analysis of efficacy', *Therapeutic Advances in Psychopharmacology*. SAGE Publications, pp. 75–99. doi: 10.1177/2045125313507739.

Calabrò, M. *et al.* (2021) 'The biological pathways of Alzheimer disease: a review', *AIMS Neuroscience*, 8(1), pp. 86–132. doi: 10.3934/Neuroscience.2021005.

Campbell, L. M. *et al.* (2020) 'Daily activities related to mobile cognitive performance in middle-aged and older adults: An ecological momentary cognitive assessment study', *JMIR mHealth and uHealth*, 8(9), p. e19579. doi: 10.2196/19579.

Carlén, M. *et al.* (2012) 'A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior', *Molecular Psychiatry*, 17(5), pp. 537–548. doi: 10.1038/mp.2011.31.

Carment, L. *et al.* (2018) 'Manual dexterity and aging: A pilot study disentangling sensorimotor from cognitive decline', *Frontiers in Neurology*, 9(OCT), pp. 1–11. doi: 10.3389/fneur.2018.00910.

Cassani, R. *et al.* (2018) 'Systematic review on resting-state EEG for Alzheimer's disease diagnosis and progression assessment', *Disease Markers*, 2018. doi: 10.1155/2018/5174815.

Cassidy, S. M., Robertson, I. H. and O'Connell, R. G. (2012) 'Retest reliability of event-related

potentials: Evidence from a variety of paradigms', *Psychophysiology*, 49(5), pp. 659–664. doi: 10.1111/j.1469-8986.2011.01349.x.

Casson, A. J. *et al.* (2008) 'Wearable EEG: What is it, why is it needed and what does it entail?', *Proceedings of the 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS'08 - 'Personalized Healthcare through Technology'*, pp. 5867–5870. doi: 10.1109/iembs.2008.4650549.

Cha, B. *et al.* (2009) 'Polarity of the first episode and time to diagnosis of bipolar I disorder', *Psychiatry Investigation*, 6(2), pp. 96–101. doi: 10.4306/pi.2009.6.2.96.

Chandler, J. J. and Paolacci, G. (2017) 'Lie for a Dime: When Most Prescreening Responses Are Honest but Most Study Participants Are Impostors', *Social Psychological and Personality Science*, 8(5), pp. 500–508. doi: 10.1177/1948550617698203.

Chandler, J. and Shapiro, D. (2016a) 'Conducting Clinical Research Using Crowdsourced Convenience Samples', *Annual Review of Clinical Psychology*, 12(1), pp. 53–81. doi: 10.1146/annurev-clinpsy-021815-093623.

Chandler, J. and Shapiro, D. (2016b) 'Conducting Clinical Research Using Crowdsourced Convenience Samples', *Annual Review of Clinical Psychology*, 12(1), pp. 53–81. doi: 10.1146/annurev-clinpsy-021815-093623.

Chaudhry, S. I. *et al.* (2010) 'Telemonitoring in Patients with Heart Failure', *New England Journal of Medicine*, 363(24), pp. 2301–2309. doi: 10.1056/nejmoa1010029.

Chelune, G. J., Bornstein, R. A. and Prifitera, A. (1990) 'The Wechsler Memory Scale-Revised: current status and applications', *Advances in psychological assessment*, 7, pp. 65–99.

Choi, J. *et al.* (2019) 'Resting-state prefrontal EEG biomarkers in correlation with MMSE scores in elderly individuals', *Scientific Reports*, 9(1), pp. 1–15. doi: 10.1038/s41598-019-46789-2.

Cintra, M. T. G. *et al.* (2018) 'Increased N200 and P300 latencies in cognitively impaired elderly

carrying ApoE ε-4 allele', *International Journal of Geriatric Psychiatry*, 33(2), pp. e221–e227. doi: 10.1002/gps.4773.

Clayson, P. E., Brush, C. J. and Hajcak, G. (2021) 'Data quality and reliability metrics for event-related potentials (ERPs): The utility of subject-level reliability', *International Journal of Psychophysiology*, 165, pp. 121–136. doi: 10.1016/j.ijpsycho.2021.04.004.

Cloninger, C. R., Svrakic, D. M. and Przybeck, T. R. (1993) 'A Psychobiological Model of Temperament and Character', *Archives of General Psychiatry*, 50(12), pp. 975–990. doi: 10.1001/archpsyc.1993.01820240059008.

Cohen, S. P. *et al.* (2018) 'Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists', *Regional Anesthesia and Pain Medicine*, 43(5), pp. 521–546. doi: 10.1097/AAP.0000000000000808.

Colic, L. *et al.* (2018) 'Delayed increase of thrombocyte levels after a single sub-anesthetic dose of ketamine – A randomized trial', *European Neuropsychopharmacology*, 28(6), pp. 701–709. doi: 10.1016/j.euroneuro.2018.03.014.

Colic, L. *et al.* (2019) 'Neuronal glutamatergic changes and peripheral markers of cytoskeleton dynamics change synchronically 24 h after sub-anaesthetic dose of ketamine in healthy subjects', *Behavioural Brain Research*, 359, pp. 312–319. doi: 10.1016/j.bbr.2018.10.021.

Coughlan, G. *et al.* (2019) 'Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease', *Proceedings of the National Academy of Sciences of the United States of America*, 116(19), pp. 9285–9292. doi: 10.1073/pnas.1901600116.

Crönlein, T. *et al.* (2013) 'Regensburg Insomnia Scale (RIS): A new short rating scale for the assessment of psychological symptoms and sleep in insomnia; Study design: Development and validation of a new short self-rating scale in a sample of 218 patients suffering from insomnia

and', *Health and Quality of Life Outcomes*, 11(1), p. 65. doi: 10.1186/1477-7525-11-65.

Crump, M. J. C., McDonnell, J. V. and Gureckis, T. M. (2013) 'Evaluating Amazon's Mechanical Turk as a Tool for Experimental Behavioral Research', *PLoS ONE*, 8(3). doi: 10.1371/journal.pone.0057410.

Cruz-Garza, J. G. *et al.* (2017) 'Deployment of mobile EEG technology in an art museum setting: Evaluation of signal quality and usability', *Frontiers in Human Neuroscience*, 11, p. 527. doi: 10.3389/fnhum.2017.00527.

Dacks, P. *et al.* (2021) 'Frontotemporal Degeneration (FTD): A Voice of the Patient Report', *The Association for Frontotemporal Degeneration (AFTD)*.

Davelaar, E. J. (2013) 'When the ignored gets bound: Sequential effects in the flanker task', *Frontiers in Psychology*, 3(JAN), pp. 1–13. doi: 10.3389/fpsyg.2012.00552.

Debener, S. *et al.* (2012) 'How about taking a low-cost, small, and wireless EEG for a walk?', *Psychophysiology*, 49(11), pp. 1617–1621. doi: 10.1111/j.1469-8986.2012.01471.x.

Dewey, B. E. *et al.* (2019) 'DeepHarmony: A deep learning approach to contrast harmonization across scanner changes', *Magnetic Resonance Imaging*, 64, pp. 160–170. doi: 10.1016/j.mri.2019.05.041.

Dimitriadis, S. I. *et al.* (2015) 'A novel biomarker of amnestic MCI based on dynamic cross-frequency coupling patterns during cognitive brain responses', *Frontiers in Neuroscience*, 9(OCT), p. 350. doi: 10.3389/fnins.2015.00350.

Dinteren, R. *et al.* (2014) 'P300 development across the lifespan: A systematic review and meta-analysis', *PLoS ONE*, 9(2). doi: 10.1371/journal.pone.0087347.

Dittrich, A., Lamparter, D. and Maurer, M. (2006) '5D-ABZ: Fragebogen zur Erfassung Aussergewöhnlicher Bewusstseinszustände. Eine kurze Einführung [5D-ASC: Questionnaire for the assessment of altered states of consciousness. A short introduction]', *Psin Plus*. Available at:

https://www.scienceopen.com/document?vid=5c0a44be-3de4-42e3-b197-f835f9b724d4.

Dohrmann, A. L. *et al.* (2017) 'EEG-arousal regulation as predictor of treatment response in patients suffering from obsessive compulsive disorder', *Clinical Neurophysiology*, 128(10), pp. 1906–1914. doi: 10.1016/j.clinph.2017.07.406.

Duman, R. S. *et al.* (2016) 'Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants', *Nature Medicine*. Nature Publishing Group, pp. 238–249. doi: 10.1038/nm.4050.

Dumont, G. J. H. *et al.* (2005) 'Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects', *British Journal of Clinical Pharmacology*, 59(5), pp. 495–510. doi: 10.1111/j.1365-2125.2005.02342.x.

Dumville, J. C., Torgerson, D. J. and Hewitt, C. E. (2006) 'Reporting attrition in randomised controlled trials', *British Medical Journal*, 332(7547), pp. 969–971. doi: 10.1136/bmj.332.7547.969.

Dustman, R. E. *et al.* (1990) 'Age and fitness effects on EEG, ERPs, visual sensitivity, and cognition', *Neurobiology of Aging*, 11(3), pp. 193–200. doi: 10.1016/0197-4580(90)90545-B.

Edgar, C. J. *et al.* (2021) 'Pilot Evaluation of the Unsupervised, At-Home Cogstate Brief Battery in ADNI-2', *Journal of Alzheimer's Disease*, 83(2), pp. 915–925. doi: 10.3233/JAD-210201.

Enriquez-Geppert, S. *et al.* (2010) 'Conflict and inhibition differentially affect the N200/P300 complex in a combined go/nogo and stop-signal task', *NeuroImage*, 51(2), pp. 877–887. doi: 10.1016/j.neuroimage.2010.02.043.

Erb, C. D., Touron, D. R. and Marcovitch, S. (2020) 'Tracking the dynamics of global and competitive inhibition in early and late adulthood: Evidence from the flanker task', *Psychology and Aging*, 35(5), pp. 729–743. doi: 10.1037/pag0000435.

Fallgatter, A. J. *et al.* (2003) 'Brain electrical dysfunction of the anterior cingulate in

schizophrenic patients', *Psychiatry Research - Neuroimaging*, 124(1), pp. 37–48. doi: 10.1016/S0925-4927(03)00072-6.

Farmer, C. A. *et al.* (2020) 'Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression', *Neuropsychopharmacology*, 45(8), pp. 1398–1404. doi: 10.1038/s41386-020-0663-6.

Feigin, V. L. *et al.* (2019) 'Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016', *The Lancet Neurology*, 18(5), pp. 459–480. doi: 10.1016/S1474-4422(18)30499-X.

Ferreira, D. *et al.* (2016) 'Electroencephalography Is a Good Complement to Currently Established Dementia Biomarkers', *Dementia and Geriatric Cognitive Disorders*, 42(1–2), pp. 80–92. doi: 10.1159/000448394.

Fiedler, P. *et al.* (2014) 'Comparison of three types of dry electrodes for electroencephalography', *Acta IMEKO*, 3(3), pp. 33–37. doi: 10.21014/acta_imeko.v3i3.94.

Fiedler, P. *et al.* (2015) 'Novel Multipin Electrode Cap System for Dry Electroencephalography', *Brain Topography*, 28(5), pp. 647–656. doi: 10.1007/s10548-015-0435-5.

Fiedler, P. *et al.* (2018) 'Contact Pressure and Flexibility of Multipin Dry EEG Electrodes', *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 26(4), pp. 750–757. doi: 10.1109/TNSRE.2018.2811752.

Fitzgerald, P. J. and Watson, B. O. (2018) 'Gamma oscillations as a biomarker for major depression: an emerging topic', *Translational Psychiatry*, 8(1), p. 177. doi: 10.1038/s41398-018-0239-y.

Fleck, J. I. *et al.* (2019) 'Distinct Functional Connectivity Patterns Are Associated With Social and Cognitive Lifestyle Factors: Pathways to Cognitive Reserve', *Frontiers in Aging Neuroscience*, 11. doi: 10.3389/fnagi.2019.00310.

Di Flumeri, G. *et al.* (2019) 'The dry revolution: Evaluation of three different eeg dry electrode types in terms of signal spectral features, mental states classification and usability', *Sensors (Switzerland)*, 19(6). doi: 10.3390/s19061365.

Franz, M. *et al.* (1998) 'German version of the Snaith-Hamilton-Pleasure-Scale (SHAPS-D): Assessing anhedonia in schizophrenic and depressive patients', *Fortschritte der Neurologie Psychiatrie*, 66(9), pp. 407–413. doi: 10.1055/s-2007-995279.

Fruehwirt, W. *et al.* (2019) 'Associations of event-related brain potentials and Alzheimer's disease severity: A longitudinal study', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 92, pp. 31–38. doi: 10.1016/j.pnpbp.2018.12.013.

Fuchs, R. *et al.* (2015) 'Measurement of physical activity and sport activity with the BSA questionnaire', *Zeitschrift fur Gesundheitspsychologie*, 23(2), pp. 60–76. doi: 10.1026/0943-8149/a000137.

Gabard-Durnam, L. J. *et al.* (2018) 'The harvard automated processing pipeline for electroencephalography (HAPPE): Standardized processing software for developmental and high-artifact data', *Frontiers in Neuroscience*, 12, p. 97. doi: 10.3389/fnins.2018.00097.

Geethanath, S. and Vaughan, J. T. (2019) 'Accessible magnetic resonance imaging: A review', *Journal of Magnetic Resonance Imaging*, 49(7), pp. e65–e77. doi: 10.1002/jmri.26638.

Gehring, W. J. *et al.* (2018) 'The Error-Related Negativity', *Perspectives on Psychological Science*, 13(2), pp. 200–204. doi: 10.1177/1745691617715310.

Geneva: World Health Organization (2017) *Global atlas of medical devices*, *WHO Medical device technical series*. Available at: https://www.who.int/medical_devices/publications/global_atlas_meddev2017/en/.

Germine, L. *et al.* (2021) 'Toward dynamic phenotypes and the scalable measurement of human behavior', *Neuropsychopharmacology*, 46(1), pp. 209–216. doi: 10.1038/s41386-020-0757-1.

Ghisletta, P. *et al.* (2018) 'Age Differences in Day-To-Day Speed-Accuracy Tradeoffs: Results from the COGITO Study', *Multivariate Behavioral Research*, 53(6), pp. 842–852. doi: 10.1080/00273171.2018.1463194.

Gilbert, J. R. and Zarate, C. A. (2020) 'Electrophysiological biomarkers of antidepressant response to ketamine in treatment-resistant depression: Gamma power and long-term potentiation', *Pharmacology Biochemistry and Behavior*, 189(1), p. 172856. doi: 10.1016/j.pbb.2020.172856.

Gillan, C. M. and Whelan, R. (2017) 'What big data can do for treatment in psychiatry', *Current Opinion in Behavioral Sciences*, 18, pp. 34–42. doi: 10.1016/j.cobeha.2017.07.003.

Gilliss, C. L. *et al.* (2001) 'Recruitment and retention of healthy minority women into community-based longitudinal research', *Journal of Women's Health and Gender-Based Medicine*, 10(1), pp. 77–85. doi: 10.1089/152460901750067142.

Greene, A. S. *et al.* (2018) 'Task-induced brain state manipulation improves prediction of individual traits', *Nature Communications*, 9(1). doi: 10.1038/s41467-018-04920-3.

Griffiths, B. *et al.* (2016) 'Brain oscillations track the formation of episodic memories in the real world', *NeuroImage*, 143, pp. 256–266. doi: 10.1016/j.neuroimage.2016.09.021.

Gronier, G. and Baudet, A. (2021) 'Psychometric Evaluation of the F-SUS: Creation and Validation of the French Version of the System Usability Scale', *International Journal of Human-Computer Interaction*, 37(16), pp. 1571–1582. doi: 10.1080/10447318.2021.1898828.

Güntekin, B. and Başar, E. (2016) 'Review of evoked and event-related delta responses in the human brain', *International Journal of Psychophysiology*, 103, pp. 43–52. doi: 10.1016/j.ijpsycho.2015.02.001.

H.N, I. A., Nugroho, P. I. and Ferdiana, R. (2015) 'Pengujian Usability Website Menggunakan System Usability Scale', *JURNAL IPTEKKOM : Jurnal Ilmu Pengetahuan & Teknologi Informasi*, 17(1), p. 31. doi: 10.33164/iptekkom.17.1.2015.31-38.

Habibzadeh Tonekabony Shad, E., Molinas, M. and Ytterdal, T. (2020) 'Impedance and Noise of Passive and Active Dry EEG Electrodes: A Review', *IEEE Sensors Journal*, 20(24), pp. 14565–14577. doi: 10.1109/JSEN.2020.3012394.

Hairston, W. D. *et al.* (2014) 'Usability of four commercially-oriented EEG systems', *Journal of Neural Engineering*, 11(4), p. 046018. doi: 10.1088/1741-2560/11/4/046018.

Hartmann, L., Sallard, E. and Spierer, L. (2016) 'Enhancing frontal top-down inhibitory control with Go/NoGo training', *Brain Structure and Function*, 221(7), pp. 3835–3842. doi: 10.1007/s00429-015-1131-7.

Hassenstab, J. *et al.* (2020) 'Remote cognitive assessment approaches in the Dominantly Inherited Alzheimer Network (DIAN)', *Alzheimer's & Dementia*, 16(S6), p. e038144. doi: 10.1002/alz.038144.

Heekeren, K. *et al.* (2008) 'Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis', *Psychopharmacology*, 199(1), pp. 77–88. doi: 10.1007/s00213-008-1129-4.

Henrich, J., Heine, S. J. and Norenzayan, A. (2010) 'The weirdest people in the world?', *Behavioral and Brain Sciences*, 33(2–3), pp. 61–83. doi: 10.1017/S0140525X0999152X.

Herrmann, C. S. and Demiralp, T. (2005) 'Human EEG gamma oscillations in neuropsychiatric disorders', *Clinical Neurophysiology*, 116(12), pp. 2719–2733. doi: 10.1016/j.clinph.2005.07.007.

Herrmann, C. S. and Knight, R. T. (2001) 'Mechanisms of human attention: Event-related potentials and oscillations', *Neuroscience and Biobehavioral Reviews*, 25(6), pp. 465–476. doi: 10.1016/S0149-7634(01)00027-6.

Herweg, N. A., Solomon, E. A. and Kahana, M. J. (2020) 'Theta Oscillations in Human Memory', *Trends in Cognitive Sciences*, 24(3), pp. 208–227. doi: 10.1016/j.tics.2019.12.006.

Hetem, L. A. B. *et al.* (2000) 'Effect of a subanesthetic dose of ketamine on memory and

conscious awareness healthy volunteers', *Psychopharmacology*, 152(3), pp. 283–288. doi: 10.1007/s002130000511.

Hinrichs, H. *et al.* (2020) 'Comparison between a wireless dry electrode EEG system with a conventional wired wet electrode EEG system for clinical applications', *Scientific Reports*, 10(1), p. 5218. doi: 10.1038/s41598-020-62154-0.

Homayoun, H. and Moghaddam, B. (2007) 'NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons', *Journal of Neuroscience*, 27(43), pp. 11496–11500. doi: 10.1523/JNEUROSCI.2213-07.2007.

Honey, G. D. *et al.* (2005) 'Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: An fMRI study', *Cerebral Cortex*, 15(6), pp. 749–759. doi: 10.1093/cercor/bhh176.

Honey, G. D. *et al.* (2006) 'The effects of a subpsychotic dose of ketamine on recognition and source memory for agency: Implications for pharmacological modelling of core symptoms of schizophrenia', *Neuropsychopharmacology*, 31(2), pp. 413–423. doi: 10.1038/sj.npp.1300846.

Honey, R. A. E. *et al.* (2003) 'Subdissociative Dose Ketamine Produces a Deficit in Manipulation but not Maintenance of the Contents of Working Memory', *Neuropsychopharmacology*, 28(11), pp. 2037–2044. doi: 10.1038/sj.npp.1300272.

Hong, L. E. *et al.* (2010) 'Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine', *Neuropsychopharmacology*, 35(3), pp. 632–640. doi: 10.1038/npp.2009.168.

Horacek, J. *et al.* (2010) 'Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: Implications for antidepressant effect', *Psychological Medicine*, 40(9), pp. 1443–1451. doi: 10.1017/S0033291709991619.

Horvath, A. *et al.* (2018) 'EEG and ERP biomarkers of Alzheimer's disease: A critical review',

Frontiers in Bioscience - Landmark, 23(2), pp. 183–220. doi: 10.2741/4587.

Howland, R. H. (2013) 'Ketmine for the treatment of depression', *Journal of Psychosocial Nursing and Mental Health Services*, 51(1), pp. 11–14. doi: 10.3928/02793695-20121219-01.

Hussain, A. *et al.* (2017) 'A usability evaluation of Lazada mobile application', *AIP Conference Proceedings*, 1891(1), p. 020059. doi: 10.1063/1.5005392.

Huster, R. J. *et al.* (2013) 'Electroencephalography of response inhibition tasks: Functional networks and cognitive contributions', *International Journal of Psychophysiology*, 87(3), pp. 217–233. doi: 10.1016/j.ijpsycho.2012.08.001.

Huys, Q. J. M. *et al.* (2016) 'German translation and validation of the cognitive style questionnaire short form (CSQ-SF-D)', *PLoS ONE*, 11(3). doi: 10.1371/journal.pone.0149530.

Inamoto, T. *et al.* (2023) 'Motor-Related Mu/Beta Rhythm in Older Adults: A Comprehensive Review', *Brain Sciences*, 13(5), p. 751. doi: 10.3390/brainsci13050751.

Janke, S. and Glöckner-Rist, A. (2014) 'Deutsche Version der Positive and Negative Affect Schedule (PANAS)', *Zusammenstellung sozialwissenschaftlicher Items und Skalen*, (October), pp. 1–15. doi: 10.6102/zis242.

Jobert, M. *et al.* (2012) 'Guidelines for the recording and evaluation of pharmaco-eeg data in man: The international pharmaco-EEG society (IPEG): The IPEG pharmaco-EEG guideline committee', *Neuropsychobiology*. Neuropsychobiology, pp. 201–220. doi: 10.1159/000343478.

Jobert, M. and Wilson, F. J. (2016) 'Advanced Analysis of Pharmaco-EEG Data in Humans', *Neuropsychobiology*, 72(3–4), pp. 165–177. doi: 10.1159/000431096.

Jodo, E. and Inoue, K. (1990) 'Effects of practice on the P300 in a Go/NoGo task', *Electroencephalography and Clinical Neurophysiology*, 76(3), pp. 249–257. doi: 10.1016/0013-4694(90)90019-G.

Johnstone, S. J. *et al.* (2017) 'Game-based combined cognitive and neurofeedback training using Focus Pocus reduces symptom severity in children with diagnosed AD/HD and subclinical AD/HD', *International Journal of Psychophysiology*, 116, pp. 32–44. doi: 10.1016/j.ijpsycho.2017.02.015.

Kam, C. D., Wilking, J. R. and Zechmeister, E. J. (2007) 'Beyond the "narrow data base": Another convenience sample for experimental research', *Political Behavior*, 29(4), pp. 415–440. doi: 10.1007/s11109-007-9037-6.

Kam, J. W. Y. *et al.* (2019) 'Systematic comparison between a wireless EEG system with dry electrodes and a wired EEG system with wet electrodes', *NeuroImage*, 184, pp. 119–129. doi: 10.1016/j.neuroimage.2018.09.012.

Kappenman, E. S. *et al.* (2021) 'ERP CORE: An open resource for human event-related potential research', *NeuroImage*, 225(May 2020), p. 117465. doi: 10.1016/j.neuroimage.2020.117465.

Kathmann, N., Frodl-Bauch, T. and Hegerl, U. (1999) 'Stability of the mismatch negativity under different stimulus and attention conditions', *Clinical Neurophysiology*, 110(2), pp. 317–323. doi: 10.1016/S1388-2457(98)00011-X.

Katsanos, C., Tselios, N. and Xenos, M. (2012) 'Perceived usability evaluation of learning management systems: A first step towards standardization of the system usability scale in Greek', in *Proceedings of the 2012 16th Panhellenic Conference on Informatics, PCI 2012*. IEEE CPS, pp. 302–307. doi: 10.1109/PCi.2012.38.

Keppler, J. S. and Conti, P. S. (2001) 'A cost analysis of positron emission tomography', *American Journal of Roentgenology*, 177(1), pp. 31–40. doi: 10.2214/ajr.177.1.1770031.

Kerr, D. C. *et al.* (2019) 'Participant engagement in and perspectives on a web-based mindfulness intervention for 9-1-1 telecommunicators: Multimethod study', *Journal of Medical Internet Research*, 21(6), p. e13449. doi: 10.2196/13449.

Kew, J. N. C. and Kemp, J. A. (2005) 'Ionotropic and metabotropic glutamate receptor structure and pharmacology', *Psychopharmacology*. Psychopharmacology (Berl), pp. 4–29. doi: 10.1007/s00213-005-2200-z.

Kirkpatrick, R. H. *et al.* (2021) 'Methodological and clinical challenges associated with biomarkers for psychiatric disease: A scoping review', *Journal of Psychiatric Research*, 143, pp. 572–579. doi: 10.1016/j.jpsychires.2020.11.023.

Kirschner, H. *et al.* (2021) 'Neural and behavioral traces of error awareness', *Cognitive, Affective and Behavioral Neuroscience*, 21(3), pp. 573–591. doi: 10.3758/s13415-020-00838-w.

Klimesch, W., Sauseng, P. and Hanslmayr, S. (2007) 'EEG alpha oscillations: The inhibition-timing hypothesis', *Brain Research Reviews*, 53(1), pp. 63–88. doi: 10.1016/j.brainresrev.2006.06.003.

De Kloet, E. R., Joëls, M. and Holsboer, F. (2005) 'Stress and the brain: From adaptation to disease', *Nature Reviews Neuroscience*, 6(6), pp. 463–475. doi: 10.1038/nrn1683.

Koenig, T., Smailovic, U. and Jelic, V. (2020) 'Past, present and future EEG in the clinical workup of dementias', *Psychiatry Research - Neuroimaging*, 306, p. 111182. doi: 10.1016/j.pscychresns.2020.111182.

Koo, B. M. and Vizer, L. M. (2019) 'Mobile Technology for Cognitive Assessment of Older Adults: A Scoping Review', *Innovation in Aging*, 3(1). doi: 10.1093/geroni/igy038.

Kramer, A. F., Wickens, C. D. and Donchin, E. (1985) 'Processing of Stimulus Properties. Evidence for Dual-Task Integrality', *Journal of Experimental Psychology: Human Perception and Performance*, 11(4), pp. 393–408. doi: 10.1037/0096-1523.11.4.393.

Krigolson, O. E. *et al.* (2017) 'Choosing MUSE: Validation of a low-cost, portable EEG system for ERP research', *Frontiers in Neuroscience*, 11(MAR). doi: 10.3389/fnins.2017.00109.

Krystal, J. H., Sanacora, G. and Duman, R. S. (2013) 'Rapid-acting glutamatergic antidepressants: The path to ketamine and beyond', *Biological Psychiatry*, 73(12), pp. 1133–1141. doi:

10.1016/j.biopsych.2013.03.026.

Kuziek, J. W. P., Shienh, A. and Mathewson, K. E. (2017) 'Transitioning EEG experiments away from the laboratory using a Raspberry Pi 2', *Journal of Neuroscience Methods*, 277, pp. 75–82. doi: 10.1016/j.jneumeth.2016.11.013.

de la Salle, S. *et al.* (2016) 'Effects of ketamine on resting-state EEG activity and their relationship to perceptual/dissociative symptoms in healthy humans', *Frontiers in Pharmacology*, 7(SEP), p. 348. doi: 10.3389/fphar.2016.00348.

Lau-Zhu, A., Lau, M. P. H. and McLoughlin, G. (2019) 'Mobile EEG in research on neurodevelopmental disorders: Opportunities and challenges', *Developmental Cognitive Neuroscience*, 36, p. 100635. doi: 10.1016/j.dcn.2019.100635.

Leach, S. *et al.* (2020) 'A Protocol for Comparing Dry and Wet EEG Electrodes During Sleep', *Frontiers in Neuroscience*, 14, p. 586. doi: 10.3389/fnins.2020.00586.

Lee, M. S. *et al.* (2013) 'Neuropsychological correlates of the P300 in patients with Alzheimer's disease', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 40(1), pp. 62–69. doi: 10.1016/j.pnpbp.2012.08.009.

Lener, M. S. *et al.* (2017) 'Glutamate and Gamma-Aminobutyric Acid Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine', *Biological Psychiatry*, 81(10), pp. 886–897. doi: 10.1016/j.biopsych.2016.05.005.

Levine, D. A. *et al.* (2015) 'Trajectory of cognitive decline after incident stroke', *JAMA - Journal of the American Medical Association*, 314(1), pp. 41–51. doi: 10.1001/jama.2015.6968.

Lewis, J. R. (2018a) 'Measuring Perceived Usability: The CSUQ, SUS, and UMUX', *International Journal of Human-Computer Interaction*, 34(12), pp. 1148–1156. doi: 10.1080/10447318.2017.1418805.

Lewis, J. R. (2018b) 'The System Usability Scale: Past, Present, and Future', *International Journal*

of Human-Computer Interaction, 34(7), pp. 577–590. doi: 10.1080/10447318.2018.1455307.

Li, M. *et al.* (2017) 'Temporal Dynamics of Antidepressant Ketamine Effects on Glutamine Cycling Follow Regional Fingerprints of AMPA and NMDA Receptor Densities', *Neuropsychopharmacology*, 42(6), pp. 1201–1209. doi: 10.1038/npp.2016.184.

Li, N. *et al.* (2010) 'mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists', *Science*, 329(5994), pp. 959–964. doi: 10.1126/science.1190287.

Light, G. A. *et al.* (2010) 'Electroencephalography (EEG) and event-related potentials (ERPs) with human participants', *Current Protocols in Neuroscience*, CHAPTER(SUPPL. 52), p. Unit. doi: 10.1002/0471142301.ns0625s52.

Light, G. A. and Näätänen, R. (2013) 'Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders', *Proceedings of the National Academy of Sciences of the United States of America*, 110(38), pp. 15175–15176. doi: 10.1073/pnas.1313287110.

Lim, Y. Y. *et al.* (2012) 'Use of the CogState brief battery in the assessment of Alzheimer's disease related cognitive impairment in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study', *Journal of Clinical and Experimental Neuropsychology*, 34(4), pp. 345–358. doi: 10.1080/13803395.2011.643227.

Lin, C. T. *et al.* (2011) 'Novel dry polymer foam electrodes for long-term EEG measurement', *IEEE Transactions on Biomedical Engineering*, 58(5), pp. 1200–1207. doi: 10.1109/TBME.2010.2102353.

Linden, D. E. J. (2005) 'The P300: Where in the brain is it produced and what does it tell us?', *Neuroscientist*, 11(6), pp. 563–576. doi: 10.1177/1073858405280524.

Linden, D. E. J. (2012) *The Challenges and Promise of Neuroimaging in Psychiatry*, *Neuron*. doi: 10.1016/j.neuron.2011.12.014.

Lindín, M. *et al.* (2013) 'Mismatch negativity (MMN) amplitude as a biomarker of sensory memory deficit in amnestic mild cognitive impairment', *Frontiers in Aging Neuroscience*, 5(NOV). doi: 10.3389/fnagi.2013.00079.

Lipsmeier, F. *et al.* (2018) 'Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial', *Movement Disorders*, 33(8), pp. 1287–1297. doi: 10.1002/mds.27376.

Lisek, M., Zylinska, L. and Boczek, T. (2020) 'Ketamine and calcium signaling—a crosstalk for neuronal physiology and pathology', *International Journal of Molecular Sciences*. Multidisciplinary Digital Publishing Institute (MDPI), pp. 1–26. doi: 10.3390/ijms21218410.

Lozano-Soldevilla, D. (2018) 'On the Physiological Modulation and Potential Mechanisms Underlying Parieto-Occipital Alpha Oscillations', *Frontiers in Computational Neuroscience*, 12(April), pp. 1–19. doi: 10.3389/fncom.2018.00023.

Lublóy, Á. *et al.* (2020) 'Exploring factors of diagnostic delay for patients with bipolar disorder: A population-based cohort study', *BMC Psychiatry*, 20(1), pp. 1–17. doi: 10.1186/S12888-020-2483-Y/TABLES/4.

Luck, S. J. *et al.* (2021) 'Standardized measurement error: A universal metric of data quality for averaged event-related potentials', *Psychophysiology*, 58(6), pp. 1–15. doi: 10.1111/psyp.13793.

Lumsden, J. *et al.* (2016) 'Gamification of cognitive assessment and cognitive training: A systematic review of applications and efficacy', *JMIR Serious Games*, 4(2), p. e11. doi: 10.2196/games.5888.

Luscher, B., Feng, M. and Jefferson, S. J. (2020) *Antidepressant mechanisms of ketamine: Focus on GABAergic inhibition*. 1st edn, *Advances in Pharmacology*. 1st edn. Elsevier Inc. doi: 10.1016/bs.apha.2020.03.002.

Lutz, A., Dunne, J. D. and Davidson, R. J. (2012) 'Meditation and the Neuroscience of

Consciousness: An Introduction', in *The Cambridge Handbook of Consciousness*. Cambridge University Press, pp. 499–552. doi: 10.1017/cbo9780511816789.020.

Maeng, S. *et al.* (2008) 'Cellular Mechanisms Underlying the Antidepressant Effects of Ketamine: Role of α-Amino-3-Hydroxy-5-Methylisoxazole-4-Propionic Acid Receptors', *Biological Psychiatry*, 63(4), pp. 349–352. doi: 10.1016/j.biopsych.2007.05.028.

Mario, B. *et al.* (2009) 'White-coat effect among older patients with suspected cognitive impairment: Prevalence and clinical implications', *International Journal of Geriatric Psychiatry*, 24(5), pp. 509–517. doi: 10.1002/gps.2145.

Maskeliunas, R. *et al.* (2016) 'Consumer-grade EEG devices: Are they usable for control tasks?', *PeerJ*, 2016(3). doi: 10.7717/peerj.1746.

Mason, W. and Suri, S. (2012) 'Conducting behavioral research on Amazon's Mechanical Turk', *Behavior Research Methods*, 44(1), pp. 1–23. doi: 10.3758/s13428-011-0124-6.

Matar, E. *et al.* (2020) 'Cognitive fluctuations in Lewy body dementia: Towards a pathophysiological framework', *Brain*, 143(1), pp. 31–46. doi: 10.1093/brain/awz311.

Mathewson, K. E., Harrison, T. J. L. and Kizuk, S. A. D. (2017) 'High and dry? Comparing active dry EEG electrodes to active and passive wet electrodes', *Psychophysiology*, 54(1), pp. 74–82. doi: 10.1111/psyp.12536.

McKeith, I. G. *et al.* (1996) 'Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop', *Neurology*, 47(5), pp. 1113–1124. doi: 10.1212/WNL.47.5.1113.

McMackin, R. *et al.* (2019) 'Dysfunction of attention switching networks in amyotrophic lateral sclerosis', *NeuroImage: Clinical*, 22(February), p. 101707. doi: 10.1016/j.nicl.2019.101707.

McWilliams, E. C. *et al.* (2021) 'Feasibility of Repeated Assessment of Cognitive Function in Older Adults Using a Wireless, Mobile, Dry-EEG Headset and Tablet-Based Games', *Frontiers in*

Psychiatry, 12, p. 979. doi: 10.3389/fpsyt.2021.574482.

Mehling, W. E. *et al.* (2012) 'The Multidimensional Assessment of Interoceptive Awareness (MAIA)', *PLoS ONE*. Edited by M. Tsakiris, 7(11), p. e48230. doi: 10.1371/journal.pone.0048230.

Michel, C. M. and Brunet, D. (2019) 'EEG source imaging: A practical review of the analysis steps', *Frontiers in Neurology*, 10(APR). doi: 10.3389/fneur.2019.00325.

Mofrad, S. A. *et al.* (2021) 'Cognitive and MRI trajectories for prediction of Alzheimer's disease', *Scientific Reports*, 11(1), pp. 1–10. doi: 10.1038/s41598-020-78095-7.

Montgomery, S. A. and Asberg, M. (1979) 'A new depression scale designed to be sensitive to change', *British Journal of Psychiatry*, 134(4), pp. 382–389. doi: 10.1192/bjp.134.4.382.

Moore, K. *et al.* (2021) 'Older adults' experiences with using wearable devices: Qualitative systematic review and meta-synthesis', *JMIR mHealth and uHealth*, 9(6), pp. 1–19. doi: 10.2196/23832.

Morgan, C. J. A. *et al.* (2004) 'Acute Effects of Ketamine on Memory Systems and Psychotic Symptoms in Healthy Volunteers', *Neuropsychopharmacology*, 29(1), pp. 208–218. doi: 10.1038/sj.npp.1300342.

Murphy, B. *et al.* (2019) 'F3-03-03: Replicating Lab Electrophysiology With Older Users in the Home, Using Gamified Dry Eeg', *Alzheimer's & Dementia*, 15, pp. P867–P867. doi: 10.1016/j.jalz.2019.06.4606.

Murphy, B. *et al.* (2020) 'Demonstration of a novel wireless EEG platform to detect the acute and long-term effects of ketamine, in the lab and in the home', in *FENS, Glasgow*.

Murrough, J. W. (2012) 'Ketamine as a novel antidepressant: From synapse to behavior', *Clinical Pharmacology and Therapeutics*, 91(2), pp. 303–309. doi: 10.1038/clpt.2011.244.

Murrough, J. W., Abdallah, C. G. and Mathew, S. J. (2017) 'Targeting glutamate signalling in

depression: Progress and prospects', *Nature Reviews Drug Discovery*, 16(7), pp. 472–486. doi: 10.1038/nrd.2017.16.

Musso, F. *et al.* (2011) 'Ketamine effects on brain function - Simultaneous fMRI/EEG during a visual oddball task', *NeuroImage*, 58(2), pp. 508–525. doi: 10.1016/j.neuroimage.2011.06.045.

Musthag, M. *et al.* (2011) 'Exploring micro-incentive strategies for participant compensation in high-burden studies', *UbiComp'11 - Proceedings of the 2011 ACM Conference on Ubiquitous Computing*, pp. 435–444. doi: 10.1145/2030112.2030170.

Muthukumaraswamy, S. D. *et al.* (2015) 'Evidence that subanesthetic doses of ketamine cause sustained disruptions of NMDA and AMPA-mediated frontoparietal connectivity in humans', *Journal of Neuroscience*, 35(33), pp. 11694–11706. doi: 10.1523/JNEUROSCI.0903-15.2015.

Näätänen, R. *et al.* (2011) 'The mismatch negativity: An index of cognitive decline in neuropsychiatric and neurological diseases and in ageing', *Brain*, 134(12), pp. 3432–3450. doi: 10.1093/brain/awr064.

Nagai, T. *et al.* (2013) 'Mismatch negativity as a "translatable" brain marker toward early intervention for psychosis: A review', *Frontiers in Psychiatry*, 4(SEP), pp. 1–10. doi: 10.3389/fpsyt.2013.00115.

Nardone, R. *et al.* (2018) 'Usefulness of EEG Techniques in Distinguishing Frontotemporal Dementia from Alzheimer's Disease and Other Dementias', *Disease Markers*, 2018, pp. 1–9. doi: 10.1155/2018/6581490.

Nasreddine, Z. S. *et al.* (2005) 'The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment', *Journal of the American Geriatrics Society*, 53(4), pp. 695–699. doi: 10.1111/j.1532-5415.2005.53221.x.

Nicosia, J., Aschenbrenner, A. J., Adams, S. L., *et al.* (2022) 'Bridging the Technological Divide: Stigmas and Challenges With Technology in Digital Brain Health Studies of Older Adults',

Frontiers in Digital Health, 4, p. 68. doi: 10.3389/fdgth.2022.880055.

Nicosia, J., Wang, B., *et al.* (2022) 'To BYOD or not: Are device latencies important for bring-your-own-device (BYOD) smartphone cognitive testing?', *Behavior Research Methods*, pp. 1–119. doi: 10.3758/s13428-022-01925-1.

Nicosia, J., Aschenbrenner, A. J., Balota, D. A., *et al.* (2022) 'Unsupervised high-frequency smartphone-based cognitive assessments are reliable, valid, and feasible in older adults at risk for Alzheimer's disease', *Journal of the International Neuropsychological Society*, (January 5), pp. 1–13. doi: 10.1017/s135561772200042x.

Niesters, M., Martini, C. and Dahan, A. (2014) 'Ketamine for chronic pain: Risks and benefits', *British Journal of Clinical Pharmacology*, 77(2), pp. 357–367. doi: 10.1111/bcp.12094.

Nieuwenhuis, S. *et al.* (2001) 'Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task', *Psychophysiology*, 38(5), pp. 752–760. doi: 10.1111/1469-8986.3850752.

Nieuwenhuis, S., Aston-Jones, G. and Cohen, J. D. (2005) 'Decision making, the P3, and the locus coeruleus-norepinephrine system', *Psychological Bulletin*, 131(4), pp. 510–532. doi: 10.1037/0033-2909.131.4.510.

Nolan, H., Whelan, R. and Reilly, R. B. (2010) 'FASTER: Fully Automated Statistical Thresholding for EEG artifact Rejection', *Journal of Neuroscience Methods*, 192(1), pp. 152–162. doi: 10.1016/j.jneumeth.2010.07.015.

Nottage, J. F. *et al.* (2023) 'The effect of ketamine and D-cycloserine on the high frequency resting EEG spectrum in humans', *Psychopharmacology*, 240(1), pp. 59–75. doi: 10.1007/s00213-022-06272-9.

Nottage, J. F. and Horder, J. (2016) 'State-of-the-Art Analysis of High-Frequency (Gamma Range) Electroencephalography in Humans', *Neuropsychobiology*, 72(3–4), pp. 219–228. doi:

10.1159/000382023.

Nugent, A. C. *et al.* (2019) 'Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects', *Molecular Psychiatry*, 24(7), pp. 1040–1052. doi: 10.1038/s41380-018-0028-2.

O'Connell, R. G. *et al.* (2007) 'The role of cingulate cortex in the detection of errors with and without awareness: A high-density electrical mapping study', *European Journal of Neuroscience*, 25(8), pp. 2571–2579. doi: 10.1111/j.1460-9568.2007.05477.x.

Olvet, D. M. and Hajcak, G. (2009) 'Reliability of error-related brain activity', *Brain Research*, 1284, pp. 89–99. doi: 10.1016/j.brainres.2009.05.079.

Ong, M. K. *et al.* (2016) 'Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure the better effectiveness after transition-heart failure (BEAT-HF) randomized clinical trial', *JAMA Internal Medicine*, 176(3), pp. 310–318. doi: 10.1001/jamainternmed.2015.7712.

Oppenheimer, D. M., Meyvis, T. and Davidenko, N. (2009) 'Instructional manipulation checks: Detecting satisficing to increase statistical power', *Journal of Experimental Social Psychology*, 45(4), pp. 867–872. doi: 10.1016/j.jesp.2009.03.009.

Oranje, B. *et al.* (2000) 'The effects of a sub-anaesthetic dose of ketamine on human selective attention', *Neuropsychopharmacology*, 22(3), pp. 293–302. doi: 10.1016/S0893-133X(99)00118-9.

Overall, J. E. and Gorham, D. R. (1962) 'The Brief Psychiatric Rating Scale', *Psychological Reports*, 10(3), pp. 799–812. doi: 10.2466/pr0.1962.10.3.799.

Owen, M. J. (2014) 'New approaches to psychiatric diagnostic classification', *Neuron*, 84(3), pp. 564–571. doi: 10.1016/j.neuron.2014.10.028.

Paitel, E. R., Samii, M. R. and Nielson, K. A. (2021) 'A systematic review of cognitive event-related

potentials in mild cognitive impairment and Alzheimer's disease', *Behavioural Brain Research*, 396(September 2020), p. 112904. doi: 10.1016/j.bbr.2020.112904.

Palva, S. and Palva, J. M. (2007) 'New vistas for α-frequency band oscillations', *Trends in Neurosciences*, 30(4), pp. 150–158. doi: 10.1016/j.tins.2007.02.001.

Pan, J., Takeshita, T. and Morimoto, K. (2000) 'Acute caffeine effect on repeatedly measured P300', *Environmental Health and Preventive Medicine*, 5(1), pp. 13–17. doi: 10.1265/ehpm.2000.13.

Paolacci, G., Chandler, J. and Ipeirotis, P. G. (2010a) 'Running experiments on Amazon mechanical turk', *Judgment and Decision Making*, 5(5), pp. 411–419. doi: 10.1017/s1930297500002205.

Paolacci, G., Chandler, J. and Ipeirotis, P. G. (2010b) 'Running experiments on Amazon mechanical turk', *Judgment and Decision Making*, 5(5), pp. 411–419.

Pavarini, S. C. I. *et al.* (2018) 'O uso do P300 como ferramenta para avaliação do processamento cognitivo em envelhecimento saudável', *Dementia e Neuropsychologia*, 12(1), pp. 1–11. doi: 10.1590/1980-57642018dn12-010001.

Pillmann, F. *et al.* (2002) 'A comparison of DSM-IV brief psychotic disorder with "positive" schizophrenia and healthy controls', *Comprehensive Psychiatry*, 43(5), pp. 385–392. doi: 10.1053/comp.2002.34629.

Pillmann, F. and Marneros, A. (2003) 'Brief and acute psychoses: The development of concepts', *History of Psychiatry*. SAGE Publications Ltd, pp. 161–177. doi: 10.1177/0957154X030142002.

Pires, L. *et al.* (2014) 'Event-Related Brain Potentials in the Study of Inhibition: Cognitive Control, Source Localization and Age-Related Modulations', *Neuropsychology Review*, 24(4), pp. 461–490. doi: 10.1007/s11065-014-9275-4.

Polich, J. (2007) 'Updating P300: An integrative theory of P3a and P3b', *Clinical Neurophysiology*,

118(10), pp. 2128–2148. doi: 10.1016/j.clinph.2007.04.019.

Polich, J. and Kok, A. (1995) 'Cognitive and biological determinants of P300: an integrative review', *Biological Psychology*, 41(2), pp. 103–146. doi: 10.1016/0301-0511(95)05130-9.

Porcaro, C. *et al.* (2019) 'P3b amplitude as a signature of cognitive decline in the older population: An EEG study enhanced by Functional Source Separation', *NeuroImage*, 184, pp. 535–546. doi: 10.1016/j.neuroimage.2018.09.057.

Powell, D. J. H. *et al.* (2017) 'Tracking daily fatigue fluctuations in multiple sclerosis: ecological momentary assessment provides unique insights', *Journal of Behavioral Medicine*, 40(5), pp. 772–783. doi: 10.1007/s10865-017-9840-4.

Prins, P. J. M. *et al.* (2011) 'Does computerized working memory training with game elements enhance motivation and training efficacy in children with ADHD?', *Cyberpsychology, behavior and social networking*, 14(3), pp. 115–122. doi: 10.1089/cyber.2009.0206.

Radüntz, T. (2018) 'Signal quality evaluation of emerging EEG devices', *Frontiers in Physiology*, 9(FEB), pp. 1–12. doi: 10.3389/fphys.2018.00098.

Rast, P., MacDonald, S. W. S. and Hofer, S. M. (2012) 'Intensive measurement designs for research on aging', *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry*, 25(2), pp. 45–55. doi: 10.1024/1662-9647/a000054.

Rehm, J. and Shield, K. D. (2019) 'Global Burden of Disease and the Impact of Mental and Addictive Disorders', *Current Psychiatry Reports*, 21(2), p. 10. doi: 10.1007/s11920-019-0997-0.

Reis, D. (2019) 'Further insights into the German version of the Multidimensional Assessment of Interoceptive Awareness (MAIA): Exploratory and Bayesian structural equation modeling approaches', *European Journal of Psychological Assessment*, 35(3), pp. 317–325. doi: 10.1027/1015-5759/a000404.

Rivolta, D. *et al.* (2015) 'Ketamine dysregulates the amplitude and connectivity of high-frequency

oscillations in cortical-subcortical networks in humans: Evidence from resting-state magnetoencephalography-recordings', *Schizophrenia Bulletin*, 41(5), pp. 1105–1114. doi: 10.1093/schbul/sbv051.

Rodrigues, P. M. *et al.* (2021) 'Lacsogram: A New EEG Tool to Diagnose Alzheimer's Disease', *IEEE Journal of Biomedical and Health Informatics*, 25(9), pp. 3384–3395. doi: 10.1109/JBHI.2021.3069789.

Roenneberg, T., Wirz-Justice, A. and Merrow, M. (2003) 'Life between clocks: Daily temporal patterns of human chronotypes', *Journal of Biological Rhythms*, 18(1), pp. 80–90. doi: 10.1177/0748730402239679.

Rogers, J. M. *et al.* (2016) 'Test-retest reliability of a single-channel, wireless EEG system', *International Journal of Psychophysiology*, 106, pp. 87–96. doi: 10.1016/j.ijpsycho.2016.06.006.

Rogers, M. A. *et al.* (2004) 'Executive and prefrontal dysfunction in unipolar depression: A review of neuropsychological and imaging evidence', *Neuroscience Research*, 50(1), pp. 1–11. doi: 10.1016/j.neures.2004.05.003.

Rosburg, T. and Kreitschmann-Andermahr, I. (2016) 'The effects of ketamine on the mismatch negativity (MMN) in humans - A meta-analysis', *Clinical Neurophysiology*, 127(2), pp. 1387–1394. doi: 10.1016/j.clinph.2015.10.062.

Sailer, M. *et al.* (2014) 'Psychological perspectives on motivation through gamification', *Interaction Design and Architecture(s)*, 19(1), pp. 28–37.

Saletu, B., Anderer, P. and Saletu-Zyhlarz, G. M. (2006) 'EEG topography and tomography (LORETA) in the classification and evaluation of the pharmacodynamics of psychotropic drugs', *Clinical EEG and Neuroscience*, 37(2), pp. 66–80. doi: 10.1177/155005940603700205.

Salisbury, D. F. *et al.* (2004) 'The NoGo P300 "anteriorization" effect and response inhibition', *Clinical Neurophysiology*, 115(7), pp. 1550–1558. doi: 10.1016/j.clinph.2004.01.028.

Saltuklaroglu, T. *et al.* (2018) 'EEG mu rhythms: Rich sources of sensorimotor information in speech processing', *Brain and Language*, 187(April 2017), pp. 41–61. doi: 10.1016/j.bandl.2018.09.005.

Salvadore, G. *et al.* (2010) 'Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine', *Neuropsychopharmacology*, 35(7), pp. 1415–1422. doi: 10.1038/npp.2010.24.

San Martín, R. (2012) 'Event-related potential studies of outcome processing and feedback-guided learning', *Frontiers in Human Neuroscience*, 6(OCTOBER 2012), pp. 1–40. doi: 10.3389/fnhum.2012.00304.

Sanacora, G. *et al.* (2017) 'A consensus statement on the use of ketamine in the treatment of mood disorders', *JAMA Psychiatry*, 74(4), pp. 399–405. doi: 10.1001/jamapsychiatry.2017.0080.

Sardi, L., Idri, A. and Fernández-Alemán, J. L. (2017) 'A systematic review of gamification in e-Health', *Journal of Biomedical Informatics*. Academic Press Inc., pp. 31–48. doi: 10.1016/j.jbi.2017.05.011.

Sauseng, P. *et al.* (2010) 'Control mechanisms in working memory: A possible function of EEG theta oscillations', *Neuroscience and Biobehavioral Reviews*, 34(7), pp. 1015–1022. doi: 10.1016/j.neubiorev.2009.12.006.

Scheidegger, M. *et al.* (2012) 'Ketamine Decreases Resting State Functional Network Connectivity in Healthy Subjects: Implications for Antidepressant Drug Action', *PLoS ONE*. Edited by S. L. Sensi, 7(9), p. e44799. doi: 10.1371/journal.pone.0044799.

Schmidt, A. *et al.* (2012) 'Mismatch negativity encoding of prediction errors predicts S-ketamine-induced cognitive impairments', *Neuropsychopharmacology*, 37(4), pp. 865–875. doi: 10.1038/npp.2011.261.

Schmidt, R. *et al.* (2019) 'Beta oscillations in working memory, executive control of movement

and thought, and sensorimotor function', *Journal of Neuroscience*, 39(42), pp. 8231–8238. doi: 10.1523/JNEUROSCI.1163-19.2019.

Schwertner, A. *et al.* (2018) 'Effects of subanesthetic ketamine administration on visual and auditory event-related potentials (ERP) in humans: A systematic review', *Frontiers in Behavioral Neuroscience*, 12, p. 70. doi: 10.3389/fnbeh.2018.00070.

Sears, D. O. (1986) 'College Sophomores in the Laboratory. Influences of a Narrow Data Base on Social Psychology's View of Human Nature', *Journal of Personality and Social Psychology*, 51(3), pp. 515–530. doi: 10.1037/0022-3514.51.3.515.

Shapiro, D. N., Chandler, J. and Mueller, P. A. (2013) 'Using mechanical turk to study clinical populations', *Clinical Psychological Science*, 1(2), pp. 213–220. doi: 10.1177/2167702612469015.

Shaw, A. D. *et al.* (2015) 'Ketamine amplifies induced gamma frequency oscillations in the human cerebral cortex', *European Neuropsychopharmacology*, 25(8), pp. 1136–1146. doi: 10.1016/j.euroneuro.2015.04.012.

Shochat, T. (2012) 'Impact of lifestyle and technology developments on sleep', *Nature and Science of Sleep*. Dove Press, pp. 19–31. doi: 10.2147/NSS.S18891.

Simonetti, O. P. and Ahmad, R. (2017) 'Low-Field Cardiac Magnetic Resonance Imaging: A Compelling Case for Cardiac Magnetic Resonance's Future', *Circulation: Cardiovascular Imaging*, 10(6). doi: 10.1161/CIRCIMAGING.117.005446.

Simpraga, S. *et al.* (2017) 'EEG machine learning for accurate detection of cholinergic intervention and Alzheimer's disease', *Scientific Reports*, 7(1), p. 5775. doi: 10.1038/s41598-017-06165-4.

Sliwinski, M. J. *et al.* (2018) 'Reliability and Validity of Ambulatory Cognitive Assessments', *Assessment*, 25(1), pp. 14–30. doi: 10.1177/1073191116643164.

Smith, J. L., Johnstone, S. J. and Barry, R. J. (2006) 'Effects of pre-stimulus processing on

subsequent events in a warned Go/NoGo paradigm: Response preparation, execution and inhibition', *International Journal of Psychophysiology*, 61(2), pp. 121–133. doi: 10.1016/j.ijpsycho.2005.07.013.

Smith, N. J. and Kutas, M. (2015) 'Regression-based estimation of ERP waveforms: I. The rERP framework', *Psychophysiology*, 52(2), pp. 157–168. doi: 10.1111/psyp.12317.

Snaith, R. P. *et al.* (1986) 'Grade scores of the Montgomery-Asberg depression and the clinical anxiety scales', *British Journal of Psychiatry*, 148(MAY), pp. 599–601. doi: 10.1192/bjp.148.5.599.

Snaith, R. P. *et al.* (1995) 'A scale for the assessment of hedonic tone. The Snaith-Hamilton Pleasure Scale', *British Journal of Psychiatry*, 167(JULY), pp. 99–103. doi: 10.1192/bjp.167.1.99.

Spielberger, C. D. *et al.* (1983) *Manual for the State-Trait Anxiety Inventory.* Consulting. Consulting Psychologists Press, Palo Alto.

Teplan, M. (2002) 'FUNDAMENTALS OF EEG MEASUREMENT M . Teplan', *Measurement Science Review*, 2(Section 2), pp. 1–11. Available at: http://www.edumed.org.br/cursos/neurociencia/MethodsEEGMeasurement.pdf.

Thapar, A., Cooper, M. and Rutter, M. (2017) 'Neurodevelopmental disorders', *The Lancet Psychiatry*. Elsevier Ltd, pp. 339–346. doi: 10.1016/S2215-0366(16)30376-5.

Thiebes, S. *et al.* (2018) 'Alterations in interhemispheric gamma-band connectivity are related to the emergence of auditory verbal hallucinations in healthy subjects during NMDA-receptor blockade', *Neuropsychopharmacology*, 43(7), pp. 1608–1615. doi: 10.1038/s41386-018-0014-z.

Thompson, L. I. *et al.* (2022) 'A highly feasible, reliable, and fully remote protocol for mobile app-based cognitive assessment in cognitively healthy older adults', *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, 14(1), p. e12283. doi: 10.1002/dad2.12283.

Tolentino, G. P. *et al.* (2011) 'Usability of serious games for health', *Proceedings - 2011 3rd International Conferenceon Games and Virtual Worlds for Serious Applications, VS-Games 2011*,

pp. 172–175. doi: 10.1109/VS-GAMES.2011.33.

Twomey, D. M. *et al.* (2015) 'The classic P300 encodes a build-to-threshold decision variable', *European Journal of Neuroscience*, 42(1), pp. 1636–1643. doi: 10.1111/ejn.12936.

Uhlhaas, P. J. and Singer, W. (2012) 'Neuronal Dynamics and Neuropsychiatric Disorders: Toward a Translational Paradigm for Dysfunctional Large-Scale Networks', *Neuron*, 75(6), pp. 963–980. doi: 10.1016/j.neuron.2012.09.004.

Umbricht, D. *et al.* (2000) 'Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: Implications for models of cognitive deficits in schizophrenia', *Archives of General Psychiatry*, 57(12), pp. 1139–1147. doi: 10.1001/archpsyc.57.12.1139.

Umbricht, D. *et al.* (2002) 'Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers', *Biological Psychiatry*, 51(5), pp. 400–406. doi: 10.1016/S0006-3223(01)01242-2.

Vaitl, D. *et al.* (2005) 'Psychobiology of altered states of consciousness', *Psychological Bulletin*. Psychol Bull, pp. 98–127. doi: 10.1037/0033-2909.131.1.98.

Valladares-Rodríguez, S. *et al.* (2016) 'Trends on the application of serious games to neuropsychological evaluation: A scoping review', *Journal of Biomedical Informatics*, 64, pp. 296–319. doi: 10.1016/j.jbi.2016.10.019.

Vanheule, S. *et al.* (2014) 'Reliability in psychiatric diagnosis with the DSM: Old wine in new barrels', *Psychotherapy and Psychosomatics*, 83(5), pp. 313–314. doi: 10.1159/000358809.

Verleger, R., Jaśkowski, P. and Wascher, E. (2005) 'Evidence for an integrative role of P3b in linking reaction to perception', *Journal of Psychophysiology*, 19(3), pp. 165–181. doi: 10.1027/0269-8803.19.3.165.

Vlisides, P. E. *et al.* (2018) 'Subanaesthetic ketamine and altered states of consciousness in humans', *British Journal of Anaesthesia*, 121(1), pp. 249–259. doi: 10.1016/j.bja.2018.03.011.

Walter, M., Li, S. and Demenescu, L. R. (2014) 'Multistage drug effects of ketamine in the treatment of major depression', *European Archives of Psychiatry and Clinical Neuroscience*, 264(1), pp. 55–65. doi: 10.1007/s00406-014-0535-3.

Wang, F. *et al.* (2016) 'Novel semi-dry electrodes for brain-computer interface applications', *Journal of Neural Engineering*, 13(4), p. 046021. doi: 10.1088/1741-2560/13/4/046021.

Watson, D., Clark, L. A. and Tellegen, A. (1988) 'Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales', *Journal of Personality and Social Psychology*, 54(6), pp. 1063–1070. doi: 10.1037/0022-3514.54.6.1063.

Watson, T. D. *et al.* (2009) 'Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission', *International Journal of Neuropsychopharmacology*, 12(3), pp. 357–370. doi: 10.1017/S1461145708009334.

Widge, A. S. *et al.* (2019) 'Electroencephalographic biomarkers for treatment response prediction in major depressive illness: A meta-analysis', *American Journal of Psychiatry*, 176(1), pp. 44–56. doi: 10.1176/appi.ajp.2018.17121358.

Widman, A. J. and McMahon, L. L. (2020) *Effects of ketamine and other rapidly acting antidepressants on hippocampal excitatory and inhibitory transmission*. 1st edn, *Advances in Pharmacology*. 1st edn. Elsevier Inc. doi: 10.1016/bs.apha.2020.05.001.

Wilks, H. *et al.* (2021) 'Sharper in the morning: Cognitive time of day effects revealed with high-frequency smartphone testing', *Journal of Clinical and Experimental Neuropsychology*, 43(8), pp. 825–837. doi: 10.1080/13803395.2021.2009447.

Wingenfeld, K. *et al.* (2010) 'The german version of the Childhood Trauma Questionnaire (CTQ):Preliminary psychometric properties', *PPmP Psychotherapie Psychosomatik Medizinische Psychologie*, 60(11), pp. 442–450. doi: 10.1055/s-0030-1247564.

Xu, J. *et al.* (2017) 'Active Electrodes for Wearable EEG Acquisition: Review and Electronics

Design Methodology', *IEEE Reviews in Biomedical Engineering*, 10(January), pp. 187–198. doi: 10.1109/RBME.2017.2656388.

Yerlikaya, D. *et al.* (2022) 'The reliability of P300 and the influence of age, gender and education variables in a 50 years and older normative sample', *International Journal of Psychophysiology*, 181, pp. 1–13. doi: 10.1016/j.ijpsycho.2022.08.002.

Yeung, N., Botvinick, M. M. and Cohen, J. D. (2004) 'The neural basis of error detection: Conflict monitoring and the error-related negativity', *Psychological Review*, pp. 931–959. doi: 10.1037/0033-295X.111.4.931.

Yeung, N. and Nieuwenhuis, S. (2009) 'Dissociating response conflict and error likelihood in anterior cingulate cortex', *Journal of Neuroscience*, 29(46), pp. 14506–14510. doi: 10.1523/JNEUROSCI.3615-09.2009.

Yeung, N. and Summerfield, C. (2012) 'Metacognition in human decision-making: Confidence and error monitoring', *Philosophical Transactions of the Royal Society B: Biological Sciences*, pp. 1310–1321. doi: 10.1098/rstb.2011.0416.

Zanos, P. *et al.* (2016) 'NMDAR inhibition-independent antidepressant actions of ketamine metabolites', *Nature*, 533(7604), pp. 481–486. doi: 10.1038/nature17998.

Zarate, C. A. *et al.* (2012) 'Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression', *Biological Psychiatry*, 72(4), pp. 331–338. doi: 10.1016/j.biopsych.2012.03.004.

Zhang, G. and Luck, S. J. (2023) 'Variations in ERP data quality across paradigms, participants, and scoring procedures', *Psychophysiology*, (February). doi: 10.1111/psyp.14264.

Zhang, X. lei *et al.* (2008) 'A NMDA receptor glycine site partial agonist, GLYX-13, simultaneously enhances LTP and reduces LTD at Schaffer collateral-CA1 synapses in hippocampus', *Neuropharmacology*, 55(7), pp. 1238–1250. doi: 10.1016/j.neuropharm.2008.08.018.

Zhou, H. and Fishbach, A. (2016) 'The pitfall of experimenting on the Web: How unattended selective attrition leads to surprising (yet false) research conclusions', *Journal of Personality and Social Psychology*, 111(4), pp. 493–504. doi: 10.1037/pspa0000056.

Zhou, W. *et al.* (2014) 'Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex', *European Psychiatry*, 29(7), pp. 419–423. doi: 10.1016/j.eurpsy.2013.10.005.