19th Biennial Conference
October 26th – 30th 2016
Nijmegen, the Netherlands
The “International Pharmaco-EEG Society, Association for Electrophysiological Brain Research in Preclinical and Clinical Pharmacology and Related Fields” (IPEG) is a non-profit organization, established in 1980 and composed of scientists and researchers actively involved in electrophysiological brain research in preclinical and clinical pharmacology, neurotoxicology and related areas of interest.
Welcome to Nijmegen,

dear attendants of the 19th IPEG meeting. Nijmegen, a 2000 year old city; Nijmegen, a Roman and a medieval city; Nijmegen, the home town of the first catholic university funded by the Faithfull to improve education of a suppressed part of the Netherlands; Nijmegen, the city that heavily suffered in WWII; Nijmegen, the home town of the Donders Institute. Nijmegen, as we hope and trust, your home town for the upcoming IPEG meeting.

As you all know, electrophysiological brain research has a long tradition going back as far as 1875 when the first report on the animal electroencephalogram (EEG) was published by Caton. The often forgotten Polish physiologist Adolf Beck was also an EEG pioneer many years before Hans Berger’s initial reports. Beck recorded electrical potentials in several brain areas evoked by peripheral sensory stimuli. Using this technique, Beck localised various centres in the brain of several animal species and described desynchronization in electrical brain potentials. He published his findings in 1890 in the German Centralblatt für Physiologie. Hans Berger did get most of the credits, most likely because he introduced the electrical brain recording method to humans, which was in the late 1920s. The EEG started having a tremendous influence both as a diagnostic instrument for sleep problems or polysomnography and in the domain of epilepsy. It was for a long time the only way to make inferences about what was going on in the brain of humans and animals, so the EEG was the most widely used instrument for brain research and certainly in the fields of sleep and epilepsy. Peripheral stimulation and recording the consequences of stimulation via ERPs became popular around the 1980s. Together with the availability of larger EEG multi-lead-multi-channel systems and more sophisticated analyses opened the way for a new application: Tomographic EEG/ERP studies. In the same period, methods were developed for the detection of the sources of electrophysiological activity in the brain. The magnetic fields produced by electrical currents occurring naturally in the brain, MEG signals, were first measured by University of Illinois physicist David Cohen in 1968. Nowadays Magnetoencephalography (MEG) is considered as a functional neuroimaging technique for mapping brain activity with most of its applications in epilepsy research, but also other applications.

The intriguing world of the effects of drugs on the EEG opened up in the sixties, a scientific area now known as pharmaco-EEG research. This was not without problems, since drugs may violate a rather fundamental perhaps somewhat hidden assumption that there is a close relation between EEG and behaviour and drugs may alter this relationship, as was nicely demonstrated by Wikler in 1952. The pharmaco-EEG has a long tradition in drug discovery and is still actively investigated to date.

In 1957, Roth and colleagues reported EEG changes associated with favourable treatment outcome to Electro Convulsive Therapy, laying the foundation of what we now consider as EEG Based Personalized Medicine, Precision Medicine and the Research Domain Criteria,
(RDoC) development. These developments highlight the value and long history of EEG as a valuable tool to quantify the effects of pharmacological treatments on the brain, and importantly, to predict their clinical outcome from the brain.

To date, there is an impressive progress in knowledge and methodology in basic EEG/MEG research regarding linear and non-linear measures, which also find their way in pharmaco-EEG studies. Needless to say that this research domain keeps on enjoying the advantageous exchange of empirical findings and insights between animal and human research. Many of the elements mentioned can be found in the program of the 19th biennial IPEG Conference.

It is therefore not so surprising that a small but dedicated society as the IPEG manages to successfully organize a series of biennial meetings on electrophysiological brain research in preclinical and clinical pharmacology and related fields. Progress in pharmaco-EEG research relies on the continuing input from a broad range of experts such as preclinical and clinical pharmacologists, psychiatrists, (neuro-)psychologists, physiologists, neurologists, biologists, clinical physicists, bio-statisticians, and computer scientists. The IPEG scientific meetings aim to bring these experts together in a colourful palette of symposia on pharmaco-EEG research to expand and update the knowledge in this increasingly complex field.

We welcome you to this, the 19th IPEG Conference, and look forward to an excellent and exciting meeting in your home town for 4 days: Nijmegen.

Gilles van Luijtenaar
Sebastian Olbrich
Marc Jobert
Leslie Prichep
Madelon Vollebregt
Martijn Arns
IPEG Training Course – Wednesday October 26th, 2016

9:00 - 9:15  Introduction

IPEG Basics: EEG and ERP’s
9:15 - 10:00  Igor Timofeev: Thalamocortical sleep oscillations
10:00 - 10:45  Leon Kenemans: Electropsychopharmacology: applying EEG and ERP to psychopharmacology
10:45 - 11:00  Coffee break

IPEG Pre-clinical applications
11:00 - 11:45  Paolo Fabene: EEG and ERP as key techniques for functional brain alterations studies.
11:45 - 12:30  Abdellah Ahnaou: Targeting EEG network oscillations: translational opportunities for drug discovery science in psychiatric and neurodegenerative disorders.
12:30 - 13:15  Lunch

IPEG Advanced EEG/ERP analysis and tomography
13:15 - 14:00  Sebastian Olbrich: Source localization using LORETA software
14:00 - 14:45  Robert Oostenveld: Analysis methods beyond standard EEG assessments.
14:45 - 15:00  Coffee break

IPEG: Clinical applications
15:00 - 15:45  Martijn Arns: EEG based personalized medicine and RDoC in ADHD and Depression.
15:45 - 16:30  Nash Boutros: Clinical applications of EEG in Psychiatry.

Evening program – Wednesday October 26th

17:00 - 17:15  Pim Drinkenburg (IPEG President), Gilles van Luitelaar / Martijn Arns (IPEG committee 2016): Presidential address and welcome.
17:15 - 17:30  Dolly Verhoeven: The history of Nijmegen
17:30 - 17:45  Gerard Meijer: The history of the Radboud University Nijmegen
17:45 - 18:00  Musical intermezzo: I Bianchi, conductor Jan Pieter Zwart.

18:00 - 20:00  Welcome reception
IPEG Conference: Thursday October 27th, 2016

8:30-9:00  Coffee light-breakfast

9.00-12.00  Fundamentals of the Electroencephalogram (EEG)

9:00-9:45  Keynote 1: Fernando Lopes da Silva: The genesis of EEG phenomena: hot topics of the last decade.

9:45-10:30  Keynote 2: Igor Timofeev: The cellular basis of sleep oscillations: What is clear and what is not.

10.30-11.00  Coffee break

11.00-11.45  Keynote 3: Ole Jensen: The allocation of resources in the brain by neuronal oscillations

11:45-12.00  Q&A Fundamentals of EEG

12:00-12:45  Lunch break

12:45-14:00  Symposium 1: Connectivity & Network analysis

Chair: Arjan Hillebrand
Jan-Mathijs Schoffelen: The dos and don’ts for electrophysiological connectivity analysis.
Alida Gouw: Magnetoencephalography as a routine diagnostic tool in memory clinic patients.
Ida Nissen: Identification of the epileptogenic zone using MEG network analysis.

14:00:14.15  Coffee break

14:15-15:30  Symposium 2: Advanced use of EEG in drug development and personalized medicine

Chair: Klaus Linkenkaer-Hansen
Sonja Simpraga: EEG biomarker integration for better decision making in clinical trials.
Michel J.A.M. van Putten: Continuous EEG and deep learning for prediction of outcome in postanoxic coma.
Claudio Babiloni: Prospects and challenges of Alzheimer’s classification using resting-state EEG rhythms.
Joerg F. Hipp: Basmisanil, a negative allosteric modulator of GABA-A alpha5 subunit-containing receptors shows target and neuronal circuit engagement in man.

15:30-16.00  Coffee break

16:00-17:30  Oral Presentations Session 1

Thijs Perenboom: Nonlinearity of the visual system assessed by cross-frequency phase coupling.
Roman Rosipal: Whole-brain time-frequency analysis of event-related potentials for the assessment of pharmacodynamic effects in the human brain.

Mehmoush Zobeiri: Dysregulation of hyperpolarization-activated inward cation current (Ih) affects thalamocortical oscillations: the role of the auxiliary subunit TRIP8b on HCN channel function in thalamic and cortical neurons.

Sofia Jacob: Advanced EEG imaging of neuronal network interactions during spatial working memory performance in rats: paving the road for pharmacological assessments

**IPEG Conference: Friday: October 28th, 2016**

8:30-9:00 Coffee light-breakfast

9:00-9:45 **Keynote 4: Sandra Loo**: Refining brain oscillatory targets for intervention in ADHD

9:45-11:15 **Symposium 3: New insights into ADHD and RDoC approaches to inattention networks**

Chairs: Madelon Vollebregt & Sandra Loo


Tieme Janssen: Attention for inhibition in ADHD: new insights with ERP source imaging.

Daniel Brandeis: Neurofeedback and pharmacological treatments in ADHD - evidence and EEG-markers.

Madelon Vollebregt: Deviant alpha oscillations as measure to help understanding the underlying mechanism of ADHD and predict treatment outcome.

11:15-11:30 Coffee break

11:30-12:30 **Symposium 4: EEG Based Personalized Medicine: An Update**

Chairs: Sebastian Olbrich & Martijn Arns


Nash Boutros: Panic attacks on the Epilepsy Spectrum.

Mark Schiller: The Psychiatric Encephalography Evaluation Registry (PEER) to personalize pharmacotherapy

12:30-13:15 Lunch
13:15-14:45  **Symposium 4 Continued.**
Sebastian Olbrich: Electrophysiological markers in the prediction of various treatment approaches in major depression and obsessive compulsive disorder.
Tabitha Iseger: The sgACC in depression: Getting at the heart of it.
Marcel Pawlowski: Heart rate variability and sleep EEG derived markers as correlates of depression and treatment response.

14.45-15:30  **Keynote 5: Roberto Pascual Marqui: title unknown.**
15.30-16.00  Coffee Break

16.00-17:30  **Symposium 5 – Translational Pharmaco-EEG: from pre-clinical (animal) to clinical?**
Chair: Pim Drinkenburg
Martien Kas: The case for translational neuroscience: how to better understand human behavior and disorders using animal EEG studies.
Clementina M. van Rijn: Anesthesia, an opportunity to measure a pharmaco-EEG par excellence

18:00-late  **Conference dinner at the historical site ‘De Waagh’ in the historic center of Nijmegen.**
IPEG Conference: Saturday October 29th, 2016

8:30-9:00 Coffee light-breakfast

9:00-10:45 Oral Presentations Session 2
Jana Koprivova: EEG functional connectivity of Brodmann area 24 in obsessive-compulsive disorder.
Laura Bonanni: Cortical network reorganization in mild and prodromal Alzheimer disease: graph theory approach on resting state EEG recordings.
Lana Donse: Sleep disturbances in obsessive-compulsive disorder: Association with response to repetitive transcranial magnetic stimulation (rTMS).
Stephanie Thiebes: Glutamatergic deficit and negative symptoms: new evidence from the ketamine model of schizophrenia.

10:45-11:00 Coffee break

11:00-12:30 Symposium 6 – Neurophysiological Assessments in Psychiatry Implications for Diagnosis, Treatment and Course.
ECNS ‘sponsored’ symposium
Chairs: Dean Salisbury & Oliver Pogarell
Oliver Pogarell: Neurophysiology Markers in Depression.
Dean Salisbury: Neurophysiological Biomarkers in First Episode Psychosis.
Bernd Saletu: Sleep and quantitative EEG in anxiety disorders.
Peter Anderer: Perception of sleep in patients with insomnia related to generalized anxiety disorder; patients with apnea and in healthy controls.

12:30-13:30 Lunch / General assembly


14:15-15:45 Symposium 7: Pharmaco-ERP
Chair: Leon Kenemans
Marieke Jepma: Catecholaminergic Regulation of Learning Rate in a Dynamic Environment.
Simone Vossel: Modulation of attentional expectancies in the human brain by cholinergic neurotransmission.
Iris Schutte: Dopamine and the cortical representation of reward.
Anke Sambeth: Optimizing the earliest memory stages: a role for acetylcholine and serotonin?

15:45-17:30  Poster session & Drinks
(note that the posters will be presented in the conference hall from Thursday morning until Saturday afternoon)

IPEG Conference: Sunday October 30th, 2016

8:30-9:00  Coffee light-breakfast

9:00-9:20  Werner Hermann Prize winner announcement

9.20-10.50  Symposium 8 – Recent advances in psychedelic research: Electrophysiological perspective.
Chair: Tomáš Páleniček
Christopher Timmermann Slater: Processing of the mismatch negativity under LSD.
Tomas Palenicke: The effects of psilocybin on human EEG, comparison with animal models.
Marta Valle: Salvinorin-A induces a unique pattern of neurophysiological effects in humans characterized by alpha suppression and widespread increases in cortical delta activity.
Martin Brunovsky: QEEG signatures predicting antidepressant response to ketamine.

11:50-11.00  Coffee break

11.05-12:05  Oral Presentations Session 3
Martin Perescis: Do cannabinoid antagonists affect cognition?
Paolo Ranzi: EEG connectivity on sources in male non-smokers after nicotine administration during resting-state.
Lyubomir I. Aftanas: Inhaling noble gas xenon in sub-narcotic dose: impact on emotion and EEG dynamics in healthy volunteers.

12:00-12:20  Farewell
Prof. Dr. med. Werner M. Herrmann (1941-2002) Memorial Grant

Sponsored by PAREXEL International

The sudden passing of Prof. Werner M. Herrmann in May 2002 was a great shock for his friends, colleagues and for everyone who regarded him as a mentor, a sounding board and a sparring partner.

Werner Herrmann was at the foremost a passionate, dedicated scientist, whose quest for excellence was enhanced by his curiosity, his initiative and his drive. He has made significant contributions through his innumerable publications and lectures and he was one of the founding members in the development of the IPEG. He also served many years as the Main Editor of NEUROPSYCHOBIOLOGY (section Pharmaco-EEG), the official journal of the IPEG.

The Werner Herrmann Memorial Grant has been established by PAREXEL International (PRXL) to encourage research in the field of neuropsychophysiology and to promote the knowledge of recent developments and advanced information of the methodology and applications of neurophysiological research in neuropsychopharmacology. The Grant of €5,000 is offered to the best contribution made by a young researcher at the biennial IPEG Conference. Half of the grant is awarded to the winner for the contribution presented at the meeting (poster or oral communication) and the other half is given after a manuscript covering the initial contribution is accepted for publication in NEUROPSYCHOBIOLOGY.

Previous Winners

IPEG Conference in Leipzig (2014):
- Sonja Simpraga (Poster): Is EEG biomarker integration the key to personalized medicine? Evidence from zygosity prediction in twins.

IPEG Conference in New York (2012):
- Carina Graversen (poster): The analgesic effect of morphine is reflected by changes in single-sweep evoked brain potentials

IPEG Conference in Prague – Czech Republic (2010):
- Sebastian Olbrich (oral presentation): EEG-based assessment of vigilance regulation in major depression and cancer-related fatigue

IPEG Conference in Rouffach – France (2008):
- Tomáš Pálenícek (poster): Quantitative EEG in glutamatergic and dopaminergic models of psychosis - animal study
- Michael Kometer (Poster): The 5-HT1A/2A Agonist Psilocybin disrupts modal object completion associated with visual hallucinations.

- Masafumi Yoshimura (oral presentation): An EEG symptom provocation study in patients with obsessive compulsive disorder
- Akinori Hozumi (poster): Effects of levodopa on mid-latency auditory evoked potentials in de novo Parkinson’s disease
- Martin Brunovsky (poster): qEEG cordance as a predictor of response to antidepressants in patients with resistant depressive disorder

IPEG Conference in Antwerp – Belgium (2004):
- Brigitte Bouwman (poster): Distinctive effects of modafinil and d-amphetamine on the homeostatic and circadian regulation of the human waking EEG

IPEG Conference Barcelona, Pain (2002):
- Florian Chapotot (oral presentation): Distinctive effects of modafinil and d-amphetamine on the homeostatic and circadian regulation of the human waking EEG
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web www.neurocaregroup.com

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visor2 solution integrates navigated TMS and EMG recording with real-time 3D visualization of stimulated brain areas. The evoked motor responses are then processed online and the calculated amplitude is projected onto an image of the stimulated cortical location to generate functional maps. The generated maps or single MEP responses can be exported in 3D image formats such as in DICOM for use in surgical navigation systems.

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inspiring technology for the human brain
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**Keynotes**

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<td>Hans-Peter Landholt</td>
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**Symposia**

**Symposium 1: Connectivity & Network analysis**

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**Symposium 2: Advanced use of EEG in drug development and personalized medicine**

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Symposium 3:  
**New insights into ADHD and RDoC approaches to inattention networks**

- **Berrie Gerrits:** EEG Cross-frequency coupling associated with attentional performance: an RDoC approach to attention.
- **Tieme Janssen:** Attention for inhibition in ADHD: new insights with ERP source imaging.
- **Daniel Brandeis:** Neurofeedback and pharmacological treatments in ADHD - evidence and EEG-markers.
- **Madelon Vollebregt:** Deviant alpha oscillations as measure to help understanding the underlying mechanism of ADHD and predict treatment outcome.

Symposium 4:  
**EEG Based Personalized Medicine: An Update**

- **Christian Sander:** Brain arousal regulation: a predictive biomarker in psychiatry.
- **Nash Boutros:** Panic attacks on the Epilepsy Spectrum.
- **Mark Schiller:** The Psychiatric Encephalography Evaluation Registry (PEER) to personalize pharmacotherapy.
- **Sebastian Olbrich:** Electrophysiological markers in the prediction of various treatment approaches in major depression and obsessive compulsive disorder.
- **Tabitha Iseger:** The sgACC in depression: Getting at the heart of it.
- **Marcel Pawlowski:** Heart rate variability and sleep EEG derived markers as correlates of depression and treatment response.

Symposium 5:  
**Translational Pharmaco-EEG: from pre-clinical (animal) to clinical?**

- **Martien Kas:** Applying integrated EEG-behavioural analyses in genetic mouse models for Autism Spectrum Disorder; the identification of translational neuronal biomarkers.
- **Clementina M. van Rijn:** Anesthesia, an opportunity to measure a pharmaco-EEG par excellence.
- **Abdellah Ahnaou:** Proof of early disintegration of functional network connectivity in the K18 seeding transgenic mouse model of tauopathy spreading from the locus coeruleus: novel opportunities for assessing pharmacological intervention therapies for Alzheimer’s disease.
- **Claudio Babiloni:** Public-private initiative to align EEG biomarkers of Alzheimer’s disease in human and mouse models for early stages of drug discovery: the achievements of IMI PharmaCog project.

Symposium 6:  
**Neurophysiological Assessments in Psychiatry Implications for Diagnosis, Treatment and Course.**

- **Oliver Pogarell:** Neurophysiology Markers in Depression.
- **Dean Salisbury:** Neuropsychological Biomarkers in First Episode Psychosis.
- **Bernd Saletu:** Sleep and quantitative EEG in anxiety disorders.
- **Peter Anderer:** Perception of sleep in patients with insomnia related to generalized anxiety disorder; patients with apnea and in healthy controls.
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### Symposium 8: Recent advances in psychedelic research: Electrophysiological perspective

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### Oral presentations

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Training course
Thalamocortical sleep oscillations.

Igor Timofeev¹,²

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In waking and sleeping states, thalamocortical system generates a variety of oscillations ranging from 0.1 Hz to hundreds of Hz. Most of them are present during NREM sleep, but slower activities prevail in this state of vigilance. Thalamocortical network is organized in a loop in which thalamocortical cells excite reticular thalamic and neocortical cells, reticular thalamic cells inhibit thalamocortical cells and corticothalamic cells excite thalamocortical and reticular thalamic cells. Despite stable anatomical connectivity, different types of oscillations preferentially originate either in neocortex or in thalamus. During sleep stage 2, spindle oscillation (9-15 Hz) is a dominant type of activity. It is well accepted that spindles originate in the thalamus via interplay of firing of reticular thalamic and thalamocortical neurons, but neocortex controls spindle generation. Spindles can be divided on fast and slow. Several properties of slow spindles do not match known mechanisms of their thalamic origin.

Slow oscillation (about 1 Hz) dominates slow-wave sleep stage. Each slow wave is composed of hyperpolarized or silent and depolarized and active state. Active states may be accompanied by spindles and higher frequency activities. Slow waves originate mainly in deep cortical layers from which they propagate to more superficial layers and they also propagate horizontally. Full expression of slow wave activities requires the presence of thalamus, although slow oscillation can be recorded in athalamic preparations. Therefore, despite the fact of preferential origin of different sleep oscillations in either neocortex or in thalamus, only the full thalamocortical network can generate sleep activities with known properties.

Support: CIHR and NSERC.
Electropsychopharmacology: applying EEG and ERP to psychopharmacology
Leon Kenemans

Electroencephalography (EEG), in particular event-related or evoked potentials (ERPs), as well as their magnetic counterparts, can yield useful supplementary information when interpreting effects of psychoactive substances on behavior. They can be used to elucidate the neurocognitive mechanisms that underlie pharmacological modulation of behavior, or they may provide additional sensitivity to detect neurocognitive effects that are not readily observable in behavioral measures. This will be illustrated by means of pertinent examples. These include elucidating the mechanisms of stimulant action remediating deficient impulse control and the role of the cannabinoid system in human working memory, as well as drug effects on sensory gating and specific aspects of visual-spatial attention. Other examples concern the added sensitivity of EEG and ERP measures, relative to that of performance measures, in detecting effects of alcohol, and more generally in monitoring and predicting vigilance and the ability to detect external signals in the immediate future. Relations between brain signals and cognitive competences are revealed by either comparing different individuals, or moment-to-moment fluctuations within individuals, or differences in state (e.g., drug-induced) within individuals.
EEG and ERP as key techniques for functional brain alterations studies
PF Fabene¹

¹Dept Neuroscience, Biomedicine and Movement, School of Medicine, University of Verona

Behavioral studies in rodents are basically based on inferring cognitive processes out of locomotor activity. In other words, we evaluate memory processes during Morris water maze, or Novel object recognition based on the time spent of the given subject in close proximity of an item, platform, or the time required to reach or leave an area of the cage/maze. By the mean of automatic scoring systems (e.g.: Ethovision, AniMaze, etc) we are provided by objective measurements, which should be in any case interpreted by the researcher. There is always a lack of direct measurement of the cognitive processes. Integration of behavioural scoring with electrical activity evaluation of different areas involved in cognitive processing can be a useful tool, to provide scientists further parameter helpful in data interpretation. We will thus discuss the integration of EEG analysis in Alzheimer’s mild cognitive impairment and acoustic ERPs in AD and epilepsy.
Targeting EEG network oscillations: translational opportunities for drug discovery science in psychiatric and neurodegenerative disorders
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Despite decades of research in psychiatric and neurodegenerative disorders, the attrition rate in clinical trials and late-stage drug discovery programs for the development of novel agents for disease interception has been unacceptably high. The major issue facing neuroscience drug discovery is that drugs that show good effectivity in preclinical models often fail to meet clinical trials endpoints. The limitations of the traditional animal-based assays prompted a resurgence of interest in rethinking animal models and their predictability and translational validity in translational neuroscience. Better translation of a biomarker and endophenotype of the disease might rapidly provide information regarding the effects of drugs on the underlying disease biology, bridge the translational gap and potentially lower the rate of clinical trial attrition. An increasing number of experimental and clinical observations suggest that those chronic brain disorders arise from structural alterations in neuronal circuits, and therefore focus has been shifted towards investigation of electrophysiological correlates of the molecular pathology, with emphasis on neural oscillations and connectivity as promising candidate biomarkers of neuronal disorders. State-of-the-art examples of pharmacological studies modeling abnormal network oscillations and disturbed connectivity of several CNS disorders will be discussed.
Source localization using LORETA software
Sebastian Olbrich

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The training course will be dedicated to the usage of LORETA software for localization of neuronal sources of EEG activity. After a brief introduction into the underlying physiology and theoretical assumptions of source localization techniques, an example of how to apply the software to EEG recordings will be shown, including limitations and caveats. Further focus will be on connectivity measures between intracortical areas as well as a short overview on statistical analysis implemented in the LORETA software.
EEG Analysis methods beyond standard assessments
Robert Oostenveld¹,²*

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Data analysis methods for EEG have shown great progress over the last two decades, partially inspired or driven by methodological advancements in adjacent research methods such as MEG, intracranial recordings and functional MRI.

In this educational session I will go over the analysis methods that can be considered part of the traditional repertoire for EEG assessments and will extend that by highlighting some recent methodological advancements for data processing.

Among others, power spectral analysis techniques using multitapers, statistical approaches based on non-parametric hypothesis, cluster based inference, robust statistics and source reconstruction techniques based on spatial filtering will be explained. The focus will be on introducing these techniques in an intuitive manner and providing pointers to data analysis tools that implement them.
At present stimulant medication, antidepressants and behavior therapy are the most often applied and accepted treatments for ADHD and Depression. However, recent large-scale studies and meta-analyses have demonstrated limitations of these treatments including reduced long-term efficacy of stimulant medication, limited efficacy of antidepressant medications and overall limited efficacy of behavioral interventions on the group level. It hence becomes obvious there is a need for a re-conceptualization of psychiatric disorders along the lines of NIMH proposed Research Domain Criteria (RDoC) or referred to as biomarkers or personalized medicine. Personalized Medicine aims to prescribe the right treatment, for the right person at the right time as opposed to the currently employed ‘one-size-fits-all’ approach. This development relies on identification of subgroups using biomarkers.

This presentation will summarize the current status of EEG based personalized medicine and present new results from large biomarker studies in depression and ADHD focused on resting-state EEG. Several results from the iSPOT study (international Study to Predict Optimized Treatment) in Depression and ADHD will be presented [1,2,3,4,5]. In iSPOT-D, 1008 depressed patients are randomized to Escitalopram, Sertraline or Venlafaxine and in iSPOT-A 336 ADHD patients are prescribed with methylphenidate and patients were assessed at baseline on resting-state EEG and other measures. Several promising biomarkers that can predict treatment response and remission using baseline biomarkers will be presented and the importance of gender differences will be discussed in more detail.

References
Clinical applications of EEG in psychiatry
Nash Boutros¹

¹University of Missouri-Kansas City

Starting with an outline of the evolving discipline of Clinical Psychiatric Electrophysiology a discussion of the value of diagnostic tests in general is given. The presentation then focuses on the well-established clinical indications of the standard EEG in the day to day practice of clinical psychiatry. Discussion will cover panic disorder, autistic spectrum disorders, and repeated aggression in some detail. Case vignettes are included to generate interactive discussion.
Keynotes
The genesis of EEG phenomena: hot topics of the last decade.
Fernando Lopes da Silva1*

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Since the turn of the century, the scope of EEG investigations became much broader, in particular due to the possibility of recording the full, physiologically relevant range of brain activities from the infra-slow to the high frequency spectral range, making use of wide dynamic direct-current (DC) coupled amplifiers, and of accurate recordings of high frequency oscillations up to hundreds of Hz. This has been denominated full-band or wide-band EEG. In this lecture, however, I focus on the high frequency EEG/MEG phenomena or High Frequency Oscillations (HFOs). These phenomena cover a number of activities that range from 60 – 80 Hz to approximately 500 Hz. Interest for these phenomena has gained momentum in the last decade. They appear in the healthy brain associated with sensory, motor and cognitive events, and also in pathological cases, particularly in epilepsy. Under the concept HFO, activities in the gamma band (30 – 70 Hz) occupy a prominent place. A variety of names are used to describe physiological EEG/MEG activity above 70 Hz such as high-gamma and the chi-band; in the context of epilepsy specific types of oscillations have been described, namely ripples (∼ 90 – 200 Hz) and fast ripples (∼ > 200 Hz), but the corresponding frequency boundaries are rather fuzzy [1]. Here I will discuss neuronal processes generating HFOs [1,2], a few relevant applications in cognitive neuroscience and in epilepsy [3], and practical questions regarding the possibilities and difficulties of reliably recording HFOs in human, and distinguishing the latter from artifacts [4].

References
Cellular basis of sleep slow oscillation: What is clear, what is not.
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The major type of activity generated by the thalamocortical system during slow-wave sleep is the slow oscillation, composed of slow waves repeated with a frequency of about 1 Hz. Each slow wave is comprised of hyperpolarized silent state, often called down state, and depolarized active state, often called up state. During wake and REM sleep cortical neurons remain in active state.

What is likely known on slow wave generation: (a) Slow oscillation is essentially cortical in origin, but it is modulated by thalamic activities. (b) Cortical slow waves in adults start more in frontal areas and propagate to other cortical areas, but multiple slow waves recorded throughout cortical mantle remain local. (c) In ferrets, mice and cats slow waves start mainly in layer 5, but in epileptic patients they originate around layer 3. (d) Silent states of slow oscillation are essentially periods of disfacilitation, but GABAergic activities can be detected in a subset of neurons prior to the onset of silent states. (e) Active states are dominated by excitatory and inhibitory synaptic activities; in anesthetized animals, these activities are balanced, in sleeping animals inhibition largely dominates active states.

What we don’t know: (a) What triggers the onset of active state? Three hypotheses are present: (1) Stochastic summation of spike-independent minis occasionally leading to the first spike that engages the whole network. (2) Intrinsic activity of layer 5 pyramidal cells (h-like current). (3) Self-organized onset of activity in groups of neurons. (b) What terminates active states? Following hypotheses are proposed: (1) Intrinsic neuronal firing frequency accommodation that decreases the overall excitatory drive. (2) Use-dependent synaptic depression. (3) Activity of Na⁺- and Ca²⁺-dependent K⁺ current. (4) Extracortical signaling. All these mechanisms are present during wake and REM sleep, but why active states are not terminated in these states of vigilance remains unclear.

Support: CIHR and NSERC.
**GABAergic modulation of neuronal oscillations in animals and humans and its consequences for working memory**

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**Background**

Networks in the brain must rely on powerful mechanism for routing and prioritizing information processing. In a larger set of attention and memory studies we have investigated the notion that alpha oscillations (9 – 12 Hz) are inhibitory and serve to route the information flow: ‘gating by inhibition’ [1]. The alpha band activity is under top-down control by areas in the dorsal attention network. As such the alpha band activity – previously believed to reflect a state of rest - serves an important role for shaping the functional architecture of the working brain. Gamma band activity (50 – 100 Hz) reflects feed-forward processing and is modulated by the alpha oscillations. In animals is has been demonstrated that GABAergic interneurons play an important role for synchronizing neural populations [2]; however, it remains unknown if these mechanistic principles generalize to human oscillations.

**Methods**

To investigate how GABAergic modulated affects gamma oscillations, we recorded ongoing brain activity using magnetoencephalography (MEG) in human subjects participating in a double-blind pharmacological study receiving placebo and lorazepam. Lorazepam is a benzodiazepine upregulating GABAergic conductance. This was done in participants while they performed a visuospatial working memory (WM) task.

**Results**

The key finding was that occipital gamma power associated with WM recognition increased with lorazepam dosage [3]. In addition, the frequency of the gamma activity decreased with dosage. This is consistent with models derived from the rat hippocampus. With respect to oscillations in the alpha band, we observed a parametrical decrease with drug dosage that also predicted a performance decrease. This is consistent with alpha oscillations reflecting functional inhibition.

**Conclusion**

We conclude that GABAergic interneurons are implicated in the generation of gamma and alpha oscillations in humans. As we will discuss these findings allow us to link neuronal dynamics to behavior in humans by embracing established animal models.

**References**

Refining Brain Oscillatory Targets for Intervention in ADHD
Sandra K Loo

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Background
Brain oscillatory patterns are increasingly used as biological markers of psychiatric disease, developmental course, and treatment response. In order to maximize effectiveness, advanced approaches should enable a mechanistic understanding of how brain rhythms carry out the cognitive and emotional processes that, when disordered, may lead to mental disorders. This will aid in the identification of interventions that show evidence of mechanism and target engagement and will increase our understanding of how efficacious interventions achieve their effect within clinical populations.

In this presentation, important considerations in the process of identifying and refining potential brain oscillatory targets that may be useful for treatment monitoring and response will be presented. For example, approaches to characterizing the significant variability and heterogeneity that exists within ADHD and typically developing populations are discussed. In addition, the need for refined measurements and signal processing techniques that increase the signal to noise ratio are described. Finally, issues such as targeting cognitive dysfunction and/or modeling developmental changes are considered.

We then describe how this approach has been implemented to identify and validate brain targets (biomarkers) in clinical trials for children with attention-deficit/hyperactivity disorder (ADHD). In addition, these data will be used to illustrate potential applications for neuromodulation approaches in ADHD as well as other neurodevelopmental disorders such as autism spectrum disorder (ASD) and Tourette’s Syndrome.

Relevance and Implications for future research
The data presented suggest that EEG-based biomarkers may be useful indices of developmental course of disorder, behavioral and cognitive functioning, and prediction of treatment response. Although the clinical utility of EEG measures is promising, more research is needed before these findings can be implemented in clinical practice.
Elucidating mechanisms of sleep-wake regulation in humans with pharmaco-genetic tools

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² Zürich Center for interdisciplinary Sleep Research, University of Zürich, Zürich, Switzerland

Epidemiological studies demonstrate that sleep-wake disorders are highly prevalent in society and rank third in the prevalence of all brain diseases. The normal alternation between sleep and wakefulness is tightly regulated, and prolonged EEG recordings show that distinct sleep and wake states reflect highly complex behaviors. Little is currently known about the molecular underpinnings of physiological sleep-wake regulation and functions. To foster our knowledge of the pathophysiology of sleep-wake disorders and their possible rational treatment, a molecular understanding of sleep-wake regulatory processes is indispensable. Accumulating evidence suggests that important aspects of sleep-wake regulation in animals and humans are genetically controlled and, thus, have a molecular basis. Consistent with this view, the combination of neurophysiologic, genetic and pharmacologic tools revealed specific roles for adenosine, dopamine and glutamate receptors and metabolic pathways in sleep-wake regulation. These studies also showed that functional allelic variation in candidate genes can profoundly affect functional aspects of sleep and wakefulness, even in healthy humans and under physiological conditions, as well as modulate individual responses to hypnotic and wake-promoting agents. These insights may provide a rationale for personalized sleep-wake pharmacotherapy (Holst et al., Annu Rev Pharmacol Toxicol, 2016). In the future, together with novel ‘omics’-studies of sleep in health and disease, they may pave the way for the discovery of new evidence-based treatments of sleep-wake pathologies such as insomnia and the pharmacological enhancement of sleep-associated brain functions such as neuronal plasticity.

Research supported by the Swiss National Science Foundation (grant # 320030_135414 & 320030_163439) and the Clinical Research Priority Program “Sleep and Health” of the University of Zürich.
The dos and don’ts for electrophysiological connectivity analysis
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In recent years it has been increasingly recognized that insight into the dynamics of interareal interactions is crucial for our understanding of normal and pathological brain function. Methodological developments and open source availability of advanced analysis tools have enabled the wider neuroscientific community to estimate a wide range of connectivity metrics from non-invasively obtained electrophysiological signals. Next to deciding on an appropriate analysis strategy, researchers are faced with the challenge to correctly interpret their findings. Volume conduction and electromagnetic field spread cause neuronal signals to be picked up by multiple channels at once, causing spurious estimates of connectivity. Comparison across experimental groups and conditions may be confounded by differences in univariate signal properties such as signal-to-noise ratio. I will illustrate some of these interpretational pitfalls and provide some recommendations that may need to be taken into account to improve the validity of the interpretation of EEG/MEG connectivity studies.
MEG as a routine diagnostic tool in memory clinic patients
Alida A Gouw1,2*, Arjan Hillebrand2, Matteo Demuru1,2, Peterjan Ris1, Philip Scheltens1, Cornelis J Stam2

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Background
Electro-encephalography (EEG) has been used as a routine diagnostic tool for patients of the Alzheimer Center Amsterdam since 2001 (1). Recently, EEG has partly been replaced by magneto-encephalography (MEG), because it may be more sensitive for pathology in disease specific regions. We investigated its discriminative value between Alzheimer’s disease (AD) and subjective cognitive decline (SCD) using a machine learning approach.

Methods
MEG was recorded in an unselected proportion of memory clinic patients as part of a routine workup. MEG data were co-registered with a head-size matched template-MRI and source-reconstructed by projection onto 90 AAL-regions using beamforming (2,3). Clinical reports were made using visual and spectral analyses, blinded for clinical information. Diagnoses were made in a weekly multi-disciplinary meeting using full clinical information and additional investigations, such as MRI and neuropsychological examination. The first 20 AD and 20 SCD patients were further analysed. Directed connectivity (directed phase transfer entropy [dPTE]) and minimum spanning tree (MST) based network measures (8–13 Hz band) were calculated per region (3–5), where the imbalance in information flow between regions was used to construct the MST. Combinations of MEG measures at eight AD-specific regions (left and right hippocampus, parahippocampal gyrus, precuneus, cuneus) were entered into random forest models to classify between patient groups.

Results
From April 2015 to July 2016, 101 patients received an MEG. Diagnoses were AD (n=26); SCD (n=24); psychiatric disorder (n=18); mild cognitive impairment (n=10); fronto-temporal dementia (n=7); Lewy body dementia (n=5); vascular dementia (n=1); and other/postponed diagnosis (n=10). One patient’s MEG diagnostic report could not be made because of movement artefacts. Her MRI and neuropsychological examination could also not be completed and she was diagnosed with severe AD based on clinical information and cerebrospinal fluid biomarkers. In the distinction between AD (age 64.8±7.9, 50% female) and SCD (age 61.4±21.8, 55% female), a random forest model using relative theta power of the eight AD regions yielded an accuracy of 0.810. Addition of dPTE for these regions increased the accuracy to 0.843. When network measures (leaf
fraction, diameter; tree hierarchy) were added to the model with theta power and dPTE an accuracy of 0.812 was found.

Conclusion
Routine diagnostic MEG is feasible in a memory clinic screening and has a high accuracy in the discrimination between AD and SCD using theta power in AD-specific regions. Directed connectivity has modest additional diagnostic value whereas network measures did not add to the diagnostic accuracy.

References
Identification of the epileptogenic zone using MEG network analysis
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Introduction
Epilepsy is increasingly seen as a brain network disorder [1-3]. Patients with epilepsy have been shown to have different networks compared to healthy controls, deviating from the optimal configuration and with abnormal network hubs [4-8]. A potent treatment for pharmacoresistant epilepsy is epilepsy surgery. The goal of epilepsy surgery is to remove or disconnect the epileptogenic zone, which renders the patient seizure-free [9]. A hypothesis about the location of the epileptogenic zone can be based on techniques such as electroencephalography (EEG) and magnetoencephalography (MEG). However, establishing a hypothesis is challenging and not always successful as currently one third of the patients continue to experience seizures after surgery [10]. New methods are therefore needed to generate more accurate hypotheses about the location of the epileptogenic zone such that more patients become seizure-free. Our aim was to develop such a new method based on network theory. We hypothesized that the epileptogenic zone coincides or connects with hubs and information senders in the network.

Methods
We analyzed eyes-closed resting-state MEG recordings of 22 patients with pharmacoresistant epilepsy. The time series in source space (virtual electrodes) were reconstructed using beamforming for 90 regions of the AAL atlas [11]. We estimated functional connectivity between those regions using phase lag index (PLI) [12] in the broadband (0.5-48Hz). We used 20 epochs of 3.28s each without artefacts or epileptiform activity. We generated the minimum spanning tree based on the PLI and calculated the betweenness centrality (an indicator of hubs) for each region. Furthermore, we assessed effective connectivity (an indicator of information senders) using the directed phase transfer entropy (dPTE) [11] for different frequency bands.

Results
ROIs with high broadband betweenness centrality (hubs) coincided with the resection cavity (or resection lobe) in 8/14 (9/14) seizure-free patients and in 0/8 (0/8) patients with remaining seizures (73% (77%) accuracy). For the effective connectivity, high dPTE values coincided with the resection cavity (or resection lobe) in 8/14 (10/14) seizure-free
patients and only in 2/8 (2/8) patients with remaining seizures (64% (73%) accuracy) in the delta band (0.5-4Hz).

Implications

Hub regions and strong senders are markers of the epileptogenic zone. These results are a first step towards a localization method that can be applied to MEG recordings even in the absence of epileptiform activity, yielding an improvement in localization and finally surgery outcome.

References
Brain disorders are a huge burden on the health care system, key issues being inaccurate diagnosis and insufficient treatment options. Hence, there is an urgent need for biomarkers that monitor disease status or therapeutic response. Current biomarkers lack the desired accuracy, because of the large variability in healthy subjects and the often subtle disease-related changes. In EEG, however, pathophysiology is often expressed in multiple ways. Here we show that an integrative approach in which any biomarker that carries complementary information about a disease or therapeutic intervention can result in an accurate diagnostic index for better decision making in clinical trials.

Recently, we showed that EEG biomarker integration improves the prediction of conversion from mild cognitive impairment to Alzheimer’s disease (AD) compared with a single-biomarker based prediction [1]. The integrative biomarker index can be used for stratification of patients at recruitment in clinical studies and for documenting and quantifying effects of intervention.

Here, we provide additional proof-of-concept that EEG-based prediction can be improved with the integrative biomarker approach in clinical trials where a drug is tested in a scopolamine challenge model in healthy subjects. Scopolamine is the most extensively studied and used model for cognitive impairment and resembles the changes seen in AD patients [2]. It is used in drug development to demonstrate the reversal of the temporary scopolamine-induced cognitive deficits by a cognition enhancing compound. For this purpose, we have developed an integrative EEG-biomarker index (mAChR index) that is optimally sensitive to the CNS effects of scopolamine, to objectively determine whether reversal of scopolamine effects by a cholinergic compound is successful. The mAChR index
yielded higher classification performance than any individual EEG biomarker with accuracy, sensitivity, specificity and precision of 90%. This significantly outperforms the single-best EEG biomarker (relative delta power). Validation on an independent dataset indicated the robustness of the index. To examine the validity of scopolamine as a cognitive impairment model, we applied this integrative index on healthy elderly controls and Alzheimer’s patients and observed that this index indeed differentiates patients from controls.

We address this by using novel features of the Neurophysiological Biomarker Toolbox (http://www.nbtwiki.net/), which employ data-mining algorithms to combine the information from multiple biomarkers. Our results demonstrate that integrating information from multiple EEG biomarkers better captures the unique phenotype of an individual patient and is a promising approach to enhance accuracy and reduce the multiple-comparisons problem when using EEG in clinical trials.

References
Continuous EEG and deep learning for outcome prediction in postanoxic coma
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Introduction
Reliable outcome prediction in approximately 50% of patients with a postanoxic encephalopathy is possible with visual interpretation of continuous EEG recorded within 24 h after cardiac arrest [2-6]. To assist in the visual assessment, we developed the Cerebral Recovery Index [7] and, more recently, a random forest classifier, showing similar performance for outcome prediction as visual assessment of the EEG [8]. Deep Learning may advance the prognostic value of EEG significantly, in part as it does not depend on ‘hand-made’ features [1,4].

Methods
We used data from the EEG database of the Medisch Spectrum Twente and Rijnstate hospitals with recordings from patients treated in the Intensive Care Unit with a postanoxic encephalopathy after a cardiac arrest. EEGs were recorded with twenty-one silver/silver chloride cup electrodes placed on the scalp according to the international 10–20 system using a Neurocenter EEG recording system (Clinical Science Systems, Voorschoten, The Netherlands) or a Nihon Kohden system (VCM Medical, the Netherlands). Neurological outcome (Cerebral performance category scores) was dichotomized as good (no or mild neurological impairment) or poor (severe neurological impairment, vegetative state or death) at 6 months after cardiac arrest.

We implemented a convolutional neural network (CNN) in python with TensorFlow on a CentOS system with the NVIDIA GTX-1080 as GPU. The input layer had dimensions 128x19 to process the raw 19-channel EEG. EEGs were analyzed using non-overlapping 2 s epochs using 5 min segments at each hour after cardiac arrest. For each patient in the validation set, we calculated the percentage of 2s epochs within the 5 min segment that is predicted as poor neurological outcome. Using ROC curves the threshold at which poor outcome could be predicted with 100% specificity was determined.

Results
After training with 131 EEGs, evaluation in an independent set with 33 patients showed that poor outcome could reliably be predicted in 67% of the patients, without false positives (specificity 100%) at=12 h after cardiac arrest; poor outcome prediction at a later instance (t=24) was not possible with a specificity of 100%. 
Discussion and Conclusion

We show feasibility of CNN to process EEG in patients with a postanoxic coma for prognostication. Pilot results show high predictive value for poor neurological outcome. As temporal evolution of EEG patterns in these patients is significant [3], recurrent neural nets may outperform convolutional networks. To understand the discriminating features, we currently explore methods for interpretation and visualization of networks.

References


Prospects and challenges of Alzheimer’s classification using resting-state EEG rhythms

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Background and aim

In the European FP7 “DECIDE” project (www.eu-decide.eu), a computing-grid infrastructure was developed to compute electroencephalographic (EEG) and other biomarkers for diagnosis and instrumental assessment of patients with Alzheimer’s disease (AD). In the framework of that project, previous evidence showed a 75.5% best accuracy in the classification of 120 Alzheimer’s disease (AD) patients with dementia and 100 matched normal elderly (Nold) subjects based on cortical source current density and linear lagged connectivity estimated by eLORETA freeware from resting state eyes-closed electroencephalographic (rsEEG) rhythms (Babiloni et al., 2016). Specifically, that accuracy was reached using the ratio between occipital delta and alpha 1 current density for a linear
univariate classifier (receiver operating characteristic curves). Here we tested a nonlinear multivariate classification (artificial neural networks, ANNs) from the same database of rsEEG markers.

Methods
Frequency bands of interest of the mentioned EEG database were delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10.5 Hz), and alpha2 (10.5-13 Hz) as an input to ANNs.

Results
ANN classification showed an accuracy of 77% using the most 4 discriminative rsEEG markers of source current density (delta/alpha1 and theta/alpha1 ratios in posterior cortical lobes). It also showed an accuracy of 72% using the most 4 discriminative rsEEG markers of source lagged linear connectivity (alphas between posterior cortical lobes). With these 8 markers combined, an accuracy of 76% was reached. Overall, the present nonlinear (ANN) multivariate classification rate cross-validated that obtained using a linear univariate classifier.

Conclusions
Although these linear rsEEG markers of cortical activity and connectivity unveil different relevant neurophysiological mechanisms underpinning cortical arousal and vigilance in AD patients, they provide quite redundant information for classification purposes. Future AD studies should use ANNs combining the present markers with other linear (i.e. directed transfer function) and nonlinear rsEEG markers to improve the classification accuracy.
Basmisanil, a negative allosteric modulator of GABA-A alpha5 subunit-containing receptors shows target and neuronal circuit engagement in man

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Background
Inhibitory GABAergic signaling plays a key role in brain function. Drugs that enhance GABA-A receptor function (e.g. Benzodiazepines) are widely used to treat conditions such as anxiety, insomnia, and epilepsy. In contrast, no inhibitors of GABA-A receptors exist for clinical use. Preclinical animal studies suggest that releasing inhibition by selectively inhibiting GABA-A alpha5 subunit-containing receptors may be beneficial in conditions of impaired cognition such Down syndrome, Schizophrenia, and Alzheimer’s disease, and may also promote functional recovery after ischemic stroke, importantly without the side effects associated to non-selective inhibitors. Here we characterize basmisanil, a novel selective negative allosteric modulator of GABA-A alpha5 receptors, in terms of in vitro pharmacology as well as receptor occupancy and EEG signature in healthy volunteers.

Methods
Radioligand binding (3H-flumazenil) and voltage-clamp electrophysiology experiments were conducted in vitro on GABA-A receptors expressed in HEK293 cells and Xenopus oocytes to demonstrate binding and functional selectivity for the GABA-A alpha5 vs. alpha1/2/3 subunit-containing receptors. A receptor occupancy study with the GABA-A alpha5 PET tracer [11C]Ro15-4513 was conducted in 10 healthy volunteers at 3 timepoints: baseline, 3, and 9 hours following 1 of 4 doses of basmisanil (2x15, 2x60, 3x130, 3x1250 mg). A separate EEG study in 12 volunteers measured at baseline, midazolam (5 mg), and 14 days of basmisanil treatment (240 mg, bid).

Results
Basmisanil (RO5186582, RG1662) bound to cloned human GABA-A alpha5 with 5-nM affinity and more than 90-fold selectivity versus alpha1/2/3 subunit-containing receptors, and concentration-dependently and reversibly inhibited the GABA-induced current of alpha5 expressing cells, yet had weak or no activity on GABA-A receptors containing other alpha subunits. Using PET, receptor occupancy was confirmed in vivo in key regions of GABA-A alpha5 subunit-containing receptors including hippocampus, insula, prefrontal
cortex, and ventral striatum. Spectral analysis of the resting EEG revealed power increase in theta to alpha-, and decrease in the beta frequency range. This EEG signature was qualitatively opposite to that of Midazolam, a non-selective positive allosteric modulator of GABA-A receptors. Basmisanil was safe and well tolerated, and no treatment-emergent epileptiform abnormalities were observed.

Discussion
Basmisanil is a highly selective GABA-A alpha5 negative allosteric modulator that reaches the desired target with good safety and tolerability, and modulates neuronal activity in humans. These data suggest basmisanil as a promising candidate drug for further clinical testing in conditions which may benefit from a reduction in excessive GABA-mediated tonic inhibition, such as cognitive impairment and stroke recovery.

Competing interests
All authors are or were employers of F. Hoffmann-La Roche Ltd.
New insights into ADHD and RDoC approaches to inattention networks
Chairs: Madelon Vollebregt & Sandra Loo

EEG Cross-frequency coupling associated with attentional performance: an RDoC approach to attention.
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The quality of attentional performance plays a crucial role in goal-directed behavior in daily life activities, cognitive task performance, and in multiple psychiatric illnesses. The Research Domain Criteria (RDoC) approach put forward by the National Institute of Mental Health aims to investigate cognitive constructs while abandoning the conventional diagnostic system of psychiatric illnesses. The current study used an RDoC approach to investigate functions underlying attentional performance.

One of the previously postulated physiologic mechanisms that could explain variance in attentional performance is the quality of interplay between neuronal networks. Various attempts to visualize this interplay have been made using different approaches. In our current study, we aimed to validate the approach of functional Independent Component Analysis (fICA) based on electroencephalograms (EEGs) for this purpose. This method yields components that reflect EEG cross-frequency coupling patterns between networks (details about the method can be found elsewhere³).

We first applied fICA to combined Eyes Open resting state EEG and EEG during an n-back task data in a large sample of healthy adults (n=1397), yielding 32 components. Secondly, we obtained individual component loadings for every subject for the two conditions as well as a difference loading score (LoadingEO−Loadingn-back) per network. Thirdly, we operationalized attentional performance by differentiating between attenders (n=704) versus non-attenders (n=320) on the n-back task and found a significant difference between groups for the difference loading score for component 10. We proposed that component 10 reflects the anti-correlated interaction of an attention network and a resting state network. This finding was cross-validated in an adolescent Attention-Deficit/Hyperactivity Disorder (ADHD) population (n=80), clinically suffering from attentional...
problems. As expected, the difference loading scores in this group was similar to the pattern observed in non-attenders. Furthermore, it was accompanied by a lower overall loading on component 10 in both conditions. The current findings seem to validate fICA as a method to visualize neuronal networks and their interactions. Combining this method with objective behavioral measures may contribute to the understanding of brain mechanisms involved in attention and attentional problems such as observed in multiple psychiatric illnesses.

References
**Attention for inhibition in ADHD: new insights with ERP source imaging**

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**Background**

Deficits in response inhibition figure prominently in models of ADHD and have been documented in cognitive [1], ERP [2] and fMRI studies [3]. Parallel to these developments, some authors have criticized the inhibition model of ADHD and associated methodology, suggesting that attentional factors confound former results [4]. In a previous fMRI study [5] we aimed to control for attentional confounds during a stop-signal task (SST). Despite this modified SST, we found evidence for reduced activation in key-areas of the inhibition network, such as the right inferior frontal gyrus (rIFG), supplementary motor area (SMA) and anterior cingulate cortex (ACC). However, according to Barkley [6], inhibition problems precede other cognitive dysfunctions, such as attentional deficits. In order to investigate this hypothesis at the brain level, both high spatial and temporal resolution are needed, which have not yet been fully integrated in one imaging technique. In the current study [7], we addressed this issue by localizing ERP components associated with response inhibition in children with ADHD.

**Methods**

Dense array ERPs (128 electrodes) were obtained for 46 children with ADHD and 51 controls during the SST. Early and late components were compared between groups. N2 and P3 components were localized with LAURA distributed linear inverse solution for each participant, and statistically compared between groups (Bonferroni-corrected based on the number of electrodes, with \(p = 0.05/128 = 0.0004\)).

**Results**

A success-related N1 modulation was only apparent in the ADHD group. N2 and P3 amplitudes were reduced in ADHD. During the successful inhibition N2, the ADHD group showed reduced activation in rIFG, SMA, and right temporoparietal junction (rTPJ), and during failed inhibition in the rIFG. During the successful inhibition P3, reduced activation was found in ACC and SMA.

**Conclusions**

Source localization of N2 revealed not only a typical inhibition network (rIFG and SMA) that was affected, but also a major hub of the ventral attention system, the rTPJ. The ventral attention system supports attentional reorienting to salient and behaviourally relevant external stimuli. The fact that this ventral attention network is implicated in the same 50ms time window (240-290ms after stop stimulus) as the inhibition network creates a challenge to Barkley’s theory of ADHD.
Competing interests
The author(s) declare no potential conflicts of interest

References
Neurofeedback and pharmacological treatments in ADHD - evidence and EEG-markers
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Scientific background/Introduction
Neurofeedback is a promising treatment for ADHD despite recent evidence cautioning that probably blinded ratings draw a less positive picture.

Theoretical framework/Hypothesis/Purpose of the work
The current presentation will focus on how recent metaanalytic evidence for neurofeedback in ADHD, address specifically studies on the add-on use and interactions with pharmacological treatment, and on the predictive EEG-based markers for neurofeedback.

Used Methods and Materials
Review of evidence from recent metaanalysis during the last 8 years [1-3] and selected individual papers on the relation to pharmacological treatment, EEG markers [4, 5] and mechanism of learning self-regulation.

Findings
The clinically relevant efficacy of neurofeedback is reduced in probably blinded ratings and compared to active or sham control conditions. This may reflect considerable unspecific effects, compromised neurofeedback quality, or lack of learning self-regulation. How neurofeedback depends on previous or concurrent pharmacological treatment is unclear. Some head to head studies report comparable or additive effects of neurofeedback and medication, but not that neurofeedback works best as an add-on or second stage treatment (beyond practical considerations). Several predictive EEG markers have been proposed but await replication.

Discussion of Relevance and Implications for future Research
The findings do not yet allow for clear recommendations as to which patients profit most from neurofeedback alone or in combination pharmacological intervention. Studies on stepped care approaches and personalized approaches – what works for whom – are urgently needed.

References
Deviant alpha oscillations as measure to help understanding the underlying mechanism of ADHD and predict treatment outcome.
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Background
Attention-deficit hyperactivity disorder (ADHD) is characterized by an inappropriate pattern of inattentiveness. Increasing evidence demonstrates that the modulation of alpha oscillations plays an important role in the allocation of attention. A failure to modulate alpha activity might therefore reflect ADHD. The first study presented here aimed to investigate alpha modulation in children with ADHD during attentional performance. The second study aimed to replicate and extend previous findings with respect to electroencephalographic (EEG) biomarkers that have shown promise in predicting treatment outcome to stimulant medication in ADHD.

Methods
For the first study [1], posterior alpha activity (8-12 Hz) was measured in 30 healthy children and 30 children with ADHD aged 7-10 years, using EEG while they performed a visuospatial covert attention task. We focused the analyses on healthy boys (N=9) and boys with ADHD (N=17). For the second study [2], data from the international Study to Predict Optimized Treatment Response in ADHD (iSPOT-A), 336 children and adolescents with ADHD were included and prescribed methylphenidate, and 158 healthy children were included. Treatment response was established after six weeks using the clinician rated ADHD-Rating Scale-IV (ADHD-RS-IV). Responders to treatment were defined as >25% improvement. The EEG Theta/Beta ratio (TBR) and alpha peak frequency (APF) were investigated as predictors for treatment outcome.

Results
In the first study, alpha activity in typically developing boys was similar to previous results of healthy adults: it decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. However, in boys with ADHD this hemispheric lateralization in the alpha band was not obvious (group contrast, p=0.18). In the second study, male-adolescent non-responders exhibited a low frontal APF (ES=0.83), whereas no differences in TBR were found between responders and non-responders. 62% of the ADHD group was classified as a responder. Responders were more often males (63% versus 51%, p=0.031), but did not differ from non-responders in age, medication dosage, and baseline severity of ADHD.
Conclusions
The first study demonstrated that the ability to modulate alpha oscillations in visual regions with the allocation of spatial attention was clearly present in healthy boys, but not in boys with ADHD. The second study demonstrated that male adolescent non-responders to methylphenidate display a lower frequency at which frontal alpha oscillations is peaking. The typical maturational changes in EEG emerging in adolescents observed in ADHD responders and controls, are absent in non-responders.

Trial registration
Clinical trial registration information; www.clinicaltrials.gov; NCT01932398 & NCT00863499

Competing interests
MA reports research grants, options/shares from Brain Resource Ltd. (Sydney, Australia) and neuroCare group and he is also a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents.

References
Brain Arousal Regulation: A predictive biomarker in psychiatry
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Arousal fundamentally impacts normal and abnormal behavior, and recently research on disturbed arousal regulation in mental disorders has attracted increasing interest. Accordingly, arousal has been implemented as a basic dimension of mental disorders in the Research Domain Criteria (RDoC) project of the National Institute of Mental Health (NIMH). The talk introduces the arousal regulation model of affective disorders and ADHD, which suggests hyper-arousal as a core pathogenetic factor in uni- and bipolar depression, and, in contrast, hypo-arousal in mania and ADHD. The model explains different clinical phenomena, as manic behavior is in parts interpreted as an autoregulatory attempt to stabilize brain arousal by creating a stimulating environment, whereas the withdrawal and sensation avoidance as well as insomnia symptoms in depression is seen as reflecting the underlying chronic hyperarousal. Many depressed patients experience themselves as subjectively fatigued and in need of rest, extended bed-times and inactivity in most cases do not result in the desired recovery but in the contrary depressive symptoms and sleep problems tend to increase. As inferable from the model, interventions that decrease arousal (e.g. antidepressants) or increase sleep need (e.g. sleep deprivation, sleep restriction) are efficient, whereas the inefficacy of stimulants has often been shown in depression. The arousal model contributes to delineating more homogenous subgroups within affective disorders and predicts response to treatment based on the respective brain arousal disturbance. Electroencephalography under resting conditions is most suitable for the assessment of brain arousal regulation, as different arousal states (also called EEG-vigilance stages) can be differentiated during the transition from high alertness to drowsiness until sleep onset according to specific EEG characteristics. The second part of the talk will introduce a computer-algorithm (Vigilance Algorithm Leipzig, VIGALL 2.1), allowing semi-automatic classification of EEG-vigilance stages during resting-EEG recordings. The time sequence of these EEG-vigilance stages indicates the individual arousal regulation of the recorded subject. The final part of the talk will outline results from current studies applying VIGALL 2.1 and investigating hypotheses derived from the arousal regulation model with regards to the usage of brain arousal regulation as a diagnostic and/or predictive biomarker in psychiatric research.

Competing interests
The author(s) declare(s) that they have no competing interests.
Panic attacks on the epilepsy spectrum
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Background
Episodic psychiatric symptoms are not uncommon and range from panic attacks to repeated violent acts. Some evidence has accumulated over the years that at least in a subset of patients exhibiting these symptoms there may be evidence for the presence of focal cortical/subcortical hyperexcitability.

Hypothesis and Purpose of the Work
In these cases, the condition could be conceptualized as an epilepsy spectrum disorder (ESD) with significant treatment implications. There is currently no clear demarcation of this category of symptoms, their prevalence, an understanding of how these symptoms occur, what is appropriate work up and possible treatments. It is being proposed here that milder degrees of increased neural excitability (i.e., a subthreshold excitation insufficient to cause seizures) may nonetheless be capable of causing observable phenotypic changes. The observable phenotypic changes depend on the degree of hyperexcitability and the location of the hyperexcitable neural tissue. The location of the abnormal neural tissue may dictate the initial manifestation of an attack resulting from activation of the hyperexcitable tissue, but the anatomical connectivity of the abnormal region will dictate the breadth of manifestations.

Methods
In this review of the literature we provide some evidence, derived from either electroencephalography (EEG) or magnetoencephalography (MEG) studies of these populations for the assumptions and proposed methods to test the advanced hypothesis. Data from a recent pilot data set from MEG in panic disorder patients is presented.

Findings
Both the literature and the pilot data point to the presence of a subgroup of panic patients who can be classified as “Epilepsy Spectrum”.

Relevance and Implications for Future Research
If the above findings are confirmed in future studies with larger sample sizes, the implications would be that it may be possible to predict response to various types of medications (e.g., selective serotonin reuptake inhibitors (SSRIs) vs. anticonvulsants). These findings would lead to more personalized treatment planning.
The Psychiatric Encephalography Evaluation Registry (PEER) to personalize pharmacotherapy

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Introduction
This presentation describes the methodology behind PEER Interactive (an objective tool based on comparison of quantitative electroencephalograms (QEEG) to an existing registry of patient outcomes). We also present interim results of an ongoing study.

Purpose
This study aims to determine whether PEER Interactive is more effective than the current standard of care in treatment of subjects suffering from depression.

Patients and methods:
This is an interim report of an ongoing, two-year prospective, randomized, double blind, controlled study to evaluate PEER Interactive in guiding medication selection in subjects with a primary diagnosis of Depression vs. standard treatment. Subjects in treatment at two military hospitals were blinded as to study group assignment and their self-report symptom ratings were also blinded. QIDS-SR16 Depression scores were the primary efficacy endpoint. 150 subjects received a quantitative electroencephalography (QEEG) exam and were randomized to either treatment as usual or PEER-Informed pharmacotherapy. Subjects in the control group were treated according to Veteran’s Administration/Department of Defense Guidelines, the current standard of care. In the experimental group, the attending physician received a PEER Report ranking the subject’s likely clinical response to on-label medications.

Results
In this post-hoc interim analysis subjects were separated into Report Followed (RF) and Report Not Followed (RNF) groups – based on the concordance between their subsequent treatment and PEER medication guidance. We thus evaluated the predictive validity of PEER recommendations. We found significantly greater improvements in depression scores (QIDS-SR16 p<0.03), reduction in suicidal ideation (CHRT-SR7 p<0.002), and PTSD score improvement (PCL-M/C p<0.04) for subjects treated with PEER-recommended medications compared to those that did not follow PEER recommendations.

Conclusion
This interim analysis suggests that an objective tool such as PEER Interactive can help improve medication selection. Consistent with results of earlier studies, it supports the hypothesis that PEER-guided treatment offers distinct advantages over the current standard of care.

References
Electrophysiological markers in the prediction of various treatment approaches in major depression and obsessive compulsive disorder
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Despite large research efforts - also in electrophysiology - within the last decades, up to now there are no clinically accepted or used biomarkers that help to diagnose affective or anxiety disorders: It seems that the discriminative abilities of clinicians concerning diagnostic decisions are fair enough. However, what is even more important than a correct diagnosis is choosing the best treatment. Here, the decisions of the clinicians are not supported by any evidence. Especially in disorders where with various treatment approaches - such as major depressive disorder (MDD) and obsessive compulsive disorder (OCD) – but a still very high percentage of non-responders to first line therapies, biomarkers could contribute to an individualized medicine with faster responses and less trial and error approaches.

Electrophysiological biomarkers provide a direct window to brain function combined with cost-effective settings and broad availability. Therefore, data on electroencephalogram (EEG) based algorithms derived from different studies will be presented that help to discriminate patients with better response to different types of treatment. Within the first part, the focus will be on predictors for treatment outcome following therapy with different types of antidepressants. Further, EEG-based biomarkers with discriminative power concerning outcome of electro-convulsive therapy (ECT) and will be shown. The second part is dedicated to treatment of OCD with cognitive-behavioral therapy, selective-serotonin inhibitors (SSRIs) or a combination of both. EEG-based biomarkers will be presented that might support the right choice of treatment.

The presentation of data will be followed by a brief outlook to what will has to come to transfer research knowledge into every day routine. Besides the need for large, prospective multicenter studies, new analytical approaches will be presented that could help to establish an individualized medicine in neuropsychiatric disorders one day.

Competing interests
Authors report no competing interests.
The sgACC in depression: Getting at the heart of it
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Major depressive disorder (MDD) is a chronic, mental disease with a remitting and relapsing course. Antidepressant medication is the most common treatment for MDD, however, the precise working mechanism underlying these treatments remains unclear. Recent neuromodulation treatments demonstrate that direct stimulation of the dorsolateral prefrontal cortex (DLPFC) and subgenual anterior cingulate (sgACC) relate to clinical improvement, suggesting connectivity alterations in this network to mediate antidepressant response, which might be similar for pharmacological treatments as well. This will be the focus of part I. The international Study to Predict Optimized Treatment in Depression (iSPOT-D) is an international multicenter study that collected EEG data for 1008 MDD patients. We investigated whether connectivity in alpha and theta frequencies within this network changed during antidepressant treatment between: patients and controls, and responders and non-responders. Women exhibited higher alpha and theta connectivity compared to males, both pre- and post-treatment. Decreased alpha connectivity after treatment was found only for male responders, while non-responders and females exhibited no changes in alpha connectivity. Furthermore, it could be useful to a priori stratify by gender for future MDD studies.

Part two focuses on functional connectivity assumptions between the DLPFC, sgACC and the vagal nerve. Preliminary results will be presented regarding a method to localize the DLPFC: neuro-cardiac-guided rTMS (NCG-rTMS). The efficacy of rTMS in the treatment of MDD has been well established in recent years, however with various methods of locating the DLPFC. It has been proposed that the efficacy of rTMS in MDD is more related to stimulating the area that is functionally connected to the sgACC rather than to specific cortical areas. Therefore, we set-out to develop and test a new method that employs the functional role of the sgACC to establish in real time if the correct cortical area is targeted. Several studies have shown that the sgACC is involved in parasympathetic regulation such as heart rate (HR) and respiration, and that neurostimulation of these areas led to HR decreases, most likely through connectivity with the nervus vagus. Based on the notion that rTMS aims to transsynaptically stimulate the sgACC, we used electrocardiogram (ECG) R-peak triggered single pulse TMS to various frontal locations to establish the correct DLPFC location.

Heart rate variability and sleep EEG derived markers as correlates of depression and treatment response
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Study Objectives
The relevance of rapid eye movement (REM) sleep for affective disorders derives from its well-established abnormalities in depressed patients, that is increased REM sleep pressure with increased frequency of rapid eye movements (REM density) as a trait marker of major depression. In this study we examined whether prefrontal theta cordance and heart rate variability (HRV) during REM sleep could represent biomarkers of antidepressant treatment response to optimize treatment outcome.

Methods
In an open-label, case-control design, thirty-three in-patients (21 females) with a depressive episode were treated with various antidepressants for four weeks. Response to treatment was defined as a ≥ 50% reduction of HAM-D score at the end of the fourth week. Sleep-EEG was recorded after the first and the fourth week of medication. Cordance was computed for prefrontal EEG channels in the theta frequency band during tonic REM sleep. HRV was derived from 3-min artefact-free electrocardiogram segments during REM sleep.

Results
First, fourteen responders had significantly higher prefrontal theta cordance as compared to nineteen non-responders after the first week of antidepressant medication. Second, HRV in REM sleep was decreased in depressive patients at week four as compared to controls (high effect size; Cohen’s d > 1). Third, HRV showed negative correlation with REM density in healthy subjects and patients at week four.

Conclusions
Our data suggest that prefrontal REM sleep-deprived cordance may predict response to antidepressant treatment in depressed patients, whereas HRV distinguishes healthy subjects from depressed patients.
Symposium 5

Translational Pharmaco-EEG: from pre-clinical (animal) to clinical?
Chair: Pim Drinkenburg

Applying integrated EEG-behavioural analyses in genetic mouse models for Autism Spectrum Disorder; the identification of translational neuronal biomarkers.
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Autism Spectrum Disorder (ASD) is a highly heterogeneous neurodevelopment disorder that is clinically defined by impaired social interaction, as well as repetitive and restricted behaviours. More than 200 ASD risk genes have been identified. Understanding the functional impact of these genetic variants will contribute to unravel clinical heterogeneity and to improve treatment efficacy. To provide clinically relevant neuronal biomarkers for specific biological subgroups, we initiated integrated EEG-behavioural analyses in selected genetic mouse models for ASD. So far, EEG data from ASD patients have shown changes in the power of brain oscillations in several frequency bands as well as in response to sensory stimuli. Although these results tell us that ASD patients have alterations at the level of brain circuits, and/or during processing of specific tasks, these biomarkers are currently not used for diagnosis of the disease.

To increase the selectively and sensitivity of neurophysiological biomarkers we analyzed the EEG of genetically modified mice during specific aspects of a behavioral task. To this end we coupled the systems used for EEG recordings and the software that tracks the location of the animal, allowing us to select parts of EEG measurements based on animal behaviour. We used Protocadherin 9 (Pcdh9) mutant mice as a model for the social interaction deficits seen in ASD patients (Bruining et al, 2015). These mice show deficits in sensorimotor development and long-term social discrimination capacity, while long-term fear conditioning is normal. Preliminary EEG results showed a decrease in gamma band oscillations in mutant mice during social interaction with both familiar and novel intruder mice. Furthermore, mutant mice showed impaired sensory information processing during an auditory mismatch negativity task. Currently, we are expanding these findings and investigate both EEG measurements and behavioral outcomes in experimental paradigms with varying degrees of difficulty for social discrimination. This way, we hope to identify translational EEG biomarkers to guide ASD patient classification and to contribute to the development of novel treatment strategies for this heterogeneous neurodevelopmental disorder.
Anesthesia, an opportunity to measure a pharmaco-EEG par excellence
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The IPEG is an association for researchers involved in electrophysiological brain research and pharmacology, and the contribution of pharmaco-EEG research to the field of neuroscience is gaining in importance. In the past few years the functions of brain circuits, i.e. functional neuroanatomical resting-state networks, have come to be on the verge of being understood. This progress is the result of close collaboration between many disciplines: neuroanatomy, psychology, physics and pharmacology, to name just a few, which are making a joint effort to understand the functioning of the brain.

In view of these developments, the EEG measured during anesthesia might hold keys to disentangle (or to the contrary perhaps to unify), behavioral, pharmacological and neurophysiological signatures of various states of behavior, especially of the difficult to quantify states of consciousness. This is because anesthesia is a drug-induced state in which patients do not have any sensation, they are unconscious. Moreover, during the whole period of anesthesia, the anesthesiologist meticulously monitors the state of wakefulness, so this procedure complies perfectly with the IPEG recommendation, which advises to measure EEG activity under vigilance-controlled conditions [4].

To induce a state of anesthesia, a variety of drugs can be used, all with quite different molecular targets. One of the still unanswered questions is: are different drugs inducing different states of anesthesia, or is anesthesia a well-described state that might be induced by modifying different stations in a hypothesized “esthesia circuit”? The contribution of mathematicians to the field of time series analysis is yielding advanced analysis algorithms with a huge potential to answer this question, since it touches on brain circuits and connectivity.

In this oral I will mini-review the literature to point out characteristic EEG and connectivity changes induced by various types of anesthetics, propofol, isoflurane and ketamine included [e.g., 1, 5]. I will illustrate the findings in the literature with our own data of both rats and humans [2, 3]. Further research questions will be proposed and discussed with the audience, in the hope to boost interest and research in our IPEG society in the EEG under anesthesia, the pharmaco-EEG par excellence.
Competing interests: None.

References

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Alzheimer’s disease (AD) is a disconnection syndrome manifested by the disruption of white matter integrity, loss of synapses and functional connectivity (FC) across different cortical and subcortical regions. Early in AD progression, tau pathology can be found in the brainstem locus coeruleus (LC) prior to its amyloid-induced exacerbation and clinical symptoms. Accordingly, the pathological process of AD is characterized by the cell-cell spread of tau pathology from the LC into the medial temporal lobe, which triggers pathological changes causing functional disconnection. Network dynamics have become a leading model to assess both the anatomical relationships (structural networks) and the coupling of dynamic neurophysiology (functional networks) linking separate brain regions.

The present study used a tau seeding model in which preformed synthetic tau fibrils (K18) were unilaterally injected into the LC of transgenic mice expressing mutant human P301L tau, equipped with multichannel electrodes in frontal cortical and CA1-CA3 hippocampal areas. This approach allows us to 1/ quantify longitudinal coherence and FC using phase-amplitude theta-gamma coupling (PAC); 2/ identify the directionality of connectivity, using lagged and extended partial direct coherence (PDC); 3/ measure pre-attentive auditory P50 potentials; 4/ investigate sleep-wake organization; and 5/ quantify phospho(p)-tau pathology in regions of interest using immunohistochemistry (AT100 antibody).

At the functional level, a decrease in spectral power at a range of frequencies in the hippocampal regions ipsilateral to the injection site is found at 2 weeks post-K18 injection, while an increase in power in contralateral hippocampal regions is hypothesized to be indicative of early compensatory mechanisms. Inter-hippocampal coherence is reduced in slow frequency oscillations and FC is significantly impaired as evidenced by: decreased intra- and inter-hemispheric hippocampal directionality of theta frequency oscillations; and reduced intra- and inter-hemispheric functional PAC strength. At the structural level, abnormal pTau aggregation is regionally specific, with AT100-positive tau detected in the pons, medulla, thalamus and cerebellum.

Ongoing assessment of pre-attentive auditory information processing, sleep-wake alterations and changes in the activity of GABAergic interneurons, which play a critical role in theta-gamma interactions, will allow further investigation into this aforementioned network dysfunction. Electrophysiological abnormalities in the hippocampus and cortex following injection of K18 into the LC convincingly support the relevance of tau pathology early in the LC. These functional alterations offer a reliable in vivo assay to test AD therapeutic agents for early intervention of tau pathology and possible prevention of the impairments in synaptic plasticity and neuronal network connectivity as seen in AD.
Public-private initiative to align EEG biomarkers of Alzheimer’s disease in human and mouse models for early stages of drug discovery: the achievements of IMI PharmaCog project

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Background and aim

In the European FP7 IMI “PharmaCog” project (Grant Agreement n°115009, www.pharmacog.org), we evaluated whether cortical electroencephalographic (EEG) rhythms in quiet wakefulness reflected prodromal Alzheimer’s disease (AD) in amnesic mild cognitive impairment (aMCI) and had a back-translational value in transgenic mouse models of Alzheimer’s disease (AD).

Methods

The research data (including human biological samples) were sourced ethically and used in line with international ethical standards. EEG rhythms were recorded in 127 aMCI subjects. Cortical sources of EEG rhythms were estimated by eLORETA package (http://www.uzh.ch/keyinst/loreta.htm). Back translation of the EEG markers was tested on on-going EEG rhythms in wild type and transgenic mouse models of AD developing an accumulation of Aβ1-42 in the brain (i.e. one mutation in PDAPP and two mutations in TASTPM).

Results

(1) Compared with the aMCI sub-group showing “negativity” to Aβ1-42/phospho tau in the cerebrospinal fluid, the aMCI sub-group showing “positivity” (prodromal AD) exhibited an abnormal delta (<4Hz) source activity in widespread cortical regions while a posterior source activity in low-frequency alpha rhythms (8-10.5 Hz) pointed to a progressive abnormality across disease progression in 2 years; (2) On-going EEG rhythms in the same frequency range were abnormal in the transgenic PDAPP and TASTPM mice when compared to the control wild-type animals. Furthermore, these EEG rhythms were modulated by an Aβ1-42 lowering agent (monoclonal antibody 3D6) administered for 4 weeks in TASTPM mice. No effect was observed in wild-type mice.

Conclusions

The results of the PharmaCog project suggest that markers of on-going cortical EEG rhythms < 12 Hz may reflect prodromal AD processes in aMCI subjects and can be back-translated to transgenic mouse models of AD. These results encouraged the use of EEG biomarkers for an early evaluation of new AD modifying drugs in transgenic mouse models of AD.
Neurophysiological Assessments in Psychiatry Implications for Diagnosis, Treatment and Course.
ECNS ‘sponsored’ symposium
Chairs: Dean Salisbury, Oliver Pogarell

Neurophysiology markers in depression - brain networks and oscillatory activity

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The neurobiological characterization of patients is a major issue in psychiatry and can help to facilitate diagnosis and therapeutic decisions; pathophysiological hypotheses with respect to brain activity or metabolism provide a scientific basis for neuropsychopharmacological approaches. The assessment of brain activity at rest or upon stimulation and the investigation of underlying neurochemical properties allow a brain functional characterisation of psychiatric disorders and thus the monitoring of treatment effects.

Dysfunctions of prefrontal neuronal circuits have been demonstrated to contribute to the pathophysiology of psychiatric disorders; in patients with depression, previous studies showed increased functional MRI and EEG connectivity. Here we present naturalistic EEG data (resting state EEG and eLORETA) of a large sample of patients with major depression (n=240) compared to gender- and age-matched healthy subjects (n=292) in terms of spectrotontemporal dynamics and brain connectivity.

EEG were recorded in resting state with closed eyes and analyzed in sensor and source space to examine functional EEG connectivity (fEEG) differences between groups. Quantitative measures of delta (δ), theta (θ), alpha (α), beta (β) and gamma (γ) power (μV²), hemispheric asymmetry, coherence, phase and eLORETA (current source density, CSD) analyses were calculated from artifact-free EEG recordings.

EEG δ power was increased in all brain regions in the group of patients, with a focus in frontal regions and increased frontal θ and α power. Marked coherence differences were detected in the δ, θ and α bands in frontal, frontal-temporal and frontal-parietal regions. Decreased coherence was found between fronto-temporal, left fronto-frontal, and centro-parietal electrodes. There were changes in phase differences in the δ, θ, α-bands between patients and healthy subjects. Differences in CSD were found for δ, θ, α-bands in the
subgenual and the rostral anterior cingulate cortex (ACC) with increased CSD in the patients.

The key finding was an increase in cortical slow-wave activity in sensor and source space in patients with depression revealing marked differences in prefrontal cortical networks. Functional δ, θ and α- connectivity (coherence and phase) were altered with a predominance in the left hemisphere.

Dysfunctions of the ACC, together with alterations in fcEEG may contribute to the pathophysiology of major depression. Future studies will explore clinical correlations, the impact of therapeutic interventions and differences to other major psychiatric disorders such as schizophrenia.
Neurophysiological Biomarkers in First Episode Psychosis
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A biomarker is an objective biological measure that can be used for health risk prediction, or for screening, diagnosis, or tracking disease progression. In psychosis research, a key recent development has been the application of a staging framework. The understanding that there is a progressive course to psychosis, including a potential prodromal phase of increasing disability before the emergence of frank psychosis, has spurred the search for screening biomarkers to indicate those truly prodromal clinical high risk for psychosis individuals that will convert to psychosis (approximately 30% in 3 years), crucial for early prophylactic treatment. Practically, true prodromal cases are rare and studies tracking conversion long and costly. To be useful for screening any disease presence biomarker must obligatorily be reduced at first psychosis. Our group has been testing various auditory-based neurophysiological tasks in first episode psychosis individuals to develop screening biomarkers for an incipient psychotic break. Here we describe several candidate biomarkers. Passive listening, simple mismatch negativity (MMN) to a rare deviant tone is not abnormal in first episode psychosis (Study 1: 29 first episode schizophrenia and 40 controls; Study 2: 35 first episode schizophrenia and 35 controls). Complex MMN tasks that depend on extraction of patterns in auditory sequences show more promise. In a series of passive tasks where the number of tones in groups were occasionally changed, we saw significant reductions of complex MMN to a rare extra tone (19 first episode schizophrenia and 19 controls). We also observed abnormalities of a slow potential that appeared to indicate the formation of each group as an acoustic object. Having participants actively count stimuli in each group revealed that a missing tone (e.g. a group of 3 instead of a group of 4) elicited an emitted P300, and that the posterior P300b component was abnormal in first episode schizophrenia (20 first episode schizophrenia and 32 controls). Using a single tone auditory evoked potential task, attention to stimuli was manipulated by having participants either press a button to every 7 tones or watch a silent video (10 first episode schizophrenia and 10 matched controls). Healthy participants modulated their N100 with attention, but first episode psychosis individuals did not. These data suggest that several neurophysiological measures may be suitable as biomarkers for the presence of psychosis. Future work will deploy these tasks in clinical high risk individuals to track whether they show promise as screening biomarkers for an incipient psychotic break.
Sleep and quantitative EEG in anxiety disorders
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Polysomnographic (PSG) investigations in nonorganic insomnia related to generalized anxiety disorder (GAD) demonstrated significantly increased wake-time during the total sleep period (TSP), more early morning awakenings, and decreased total sleep time (TST) and sleep efficiency as compared with normals. Sleep architecture showed decreased S2 % and increased S1, S3+S4 %, but no differences in REM measures. Subjective sleep quality and morning thymopsychic measures were deteriorated; noopsychic performance was rather good. Benzodiazepine therapy induced opposite changes.

PSG investigations in nonorganic insomnia related to panic disorder demonstrated decreased sleep efficiency, TST and S2, and increased middle and late insomnia (S1, S3+S4), snoring and periodic leg movements as compared with controls, but no differences in REM variables. Subjective sleep quality, morning drive and fine motor activity were deteriorated. Evening and morning blood pressure and evening pulse rate were elevated. As compared with placebo, alprazolam 0.5 mg induced changes opposite to the differences observed between patients and controls before treatment, thereby normalizing sleep and awakening quality. This points to a key-lock principle in the treatment of insomnia due to anxiety disorders and neurophysiologically visualizes processes at the receptor level (e.g. benzodiazepine agonists vs. inverse agonists).

Daytime EEG mapping studies demonstrated in GAD patients increased total power; absolute delta/theta, absolute and relative alpha power and decreased relative beta power; reflecting neurophysiological hypervigilance.

Anti-anxiety drugs such as the classical benzodiazepine tranquilizers induced - as compared with placebo - changes opposite to the differences between anxiety patients and normal controls, which confirms the key-lock principle.
Daytime tranquilizers (e.g. 30 mg clobazam) decreased total power; absolute and relative delta/theta and alpha power and increased absolute and relative beta power. The delta/theta centroid was slowed, as partly was the beta centroid, while the total centroid was accelerated.

Nighttime tranquilizers (e.g. lorazepam) attenuated total power; decreased absolute alpha and increased absolute beta power; increased relative delta/theta and beta and decreased alpha power; slowed the delta/theta centroid and accelerated the alpha and total centroid.
Low-resolution brain electromagnetic tomography (LORETA) in GAD patients showed that changes after anxiolytic sedatives (e.g. lorazepam and Somnium®), as compared with placebo, were in certain brain regions opposite to the differences between baseline recordings in these patients and normal controls. These novel neurophysiological findings demonstrate the mode of action of the drugs at the benzodiazepine receptor (benzodiazepine agonist vs. inverse benzodiazepine agonists) and suggest that treatment is causal rather than symptomatic. Thus, LORETA reveals target regions of psychotropic drugs and shows a key-lock principle in the diagnosis of anxiety disorders and their treatment with benzodiazepines.
Perception of sleep in patients with insomnia related to generalized anxiety disorder, patients with apnea and in healthy controls

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Background
Although sleep research has been trying to elucidate the relations between objective and subjective sleep and awakening quality for five decades, findings have often been controversial. This might be due to the lack of large data sets, to the differences between different sleep disorders and to the inter-individual differences in sleep perception per se.

Objectives
The aim of the present study was to investigate relations between objective and subjective sleep variables in a large number of healthy subjects as well as in 2 clinically relevant patient groups, i.e. nonorganic insomnia in generalized anxiety disorder (insomnia/GAD) and sleep apnea.

Material and Methods
One hundred and seventy-seven healthy subjects (94 females, 83 males, aged 20 – 95 years), 61 insomniac GAD patients (32 females, 29 males, aged 21 – 66 years) and 51 apnea patients (7 females, 44 males, aged 29 – 73 years) underwent two polysomnographic nights analyzed by the Somnolyzer [1] and completed the self-rating scale for sleep and awakening quality [2].

Results
Patients with insomnia/GAD underestimated their sleep efficiency in both nights (objective sleep efficiency index (SEI) 77% and 84% versus subjective SEI 57% and 64% for adaptation and baseline night, respectively, p<0.001 Wilcoxon test). Apnea patients showed no differences between subjective and objective SEI (objective 80% and 87% versus subjective 79% and 86%). Healthy controls – specifically males and subjects older than 60 years – overestimated their sleep efficiency in the adaptation night (objective 80% and 86% versus subjective 84% and 87%, p<0.001 for night 1). Correlation analysis between objective and subjective SEI on change values from adaptation to baseline night revealed highly significant correlations for all three groups (r=.77 for GAD, r=.57 for apnea and r=.51 in healthy controls). Interestingly, the regression lines go through the origin in all three groups, i.e. no change in objective SEI is perceived as no change in subjective SEI.
Conclusions
Relations between subjective and objective sleep efficiency are influenced by age, gender and the type of sleep disorder. In correlation analyses, the problem of inter-individual judgements of sleep perception can be reduced by using change values between adaptation and baseline nights rather than raw values. The variety of correlations requires a parallel evaluation of subjective and objective variables as they are not interchangeable.

Peter Anderer, Georg Gruber, Silvia Parapatics and Georg Dorffner are employees of The Siesta Group Schlafanalyse GmbH. Gerda M Saletu-Zyhlarz and Bernd Saletu have no competing interests

References
Catecholaminergic regulation of learning rate in a dynamic environment

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Adaptive behavior in a changing world requires flexibly adapting one’s rate of learning to the rate of environmental change. Recent studies have examined the computational mechanisms by which various environmental factors determine the impact of new outcomes on existing beliefs (i.e., the ‘learning rate’). However, the brain mechanisms, and in particular the neuromodulators, involved in this process are still largely unknown. The brain-wide neurophysiological effects of the catecholamines norepinephrine and dopamine on stimulus-evoked cortical responses suggest that the catecholamine systems are well positioned to regulate learning about environmental change, but more direct evidence for a role of this system is scant. Here, we report evidence from a study employing pharmacology, scalp electrophysiology and computational modeling (N=32) that suggests an important role for catecholamines in learning-rate regulation. We found that the P3 component of the EEG—an electrophysiological index of outcome-evoked phasic catecholamine release in the cortex-predicted learning rate, and formally mediated the effect of prediction-error magnitude on learning rate. P3 amplitude also mediated the effects of two computational variables—capturing the unexpectedness of an outcome and the uncertainty of a preexisting belief—on learning rate. Furthermore, a pharmacological manipulation of catecholamine activity affected learning rate following unanticipated task changes, in a way that depended on participants’ baseline learning rate. Our findings provide converging evidence for a causal role of the human catecholamine systems in learning-rate regulation as a function of environmental change.
Modulation of attentional expectancies in the human brain by cholinergic neurotransmission

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Many psychopharmacological animal and human studies suggest a pivotal role of acetylcholine for attentional functions. However, the exact mechanisms whereby the cholinergic neurotransmitter system contributes to attentional processing remain poorly understood. Here, we investigated the effect of the pro-cholinergic drug galantamine on expectation-guided attentional processing by characterizing the effects of predictions and uncertainty in a novel version of Posner’s location-cueing paradigm. Application of a computational model allowed us to characterize the cholinergic modulation of attention formally, in terms of hierarchical Bayesian inference. This model can be regarded as a variant of predictive coding – in which updates are determined by prediction errors that are weighted by their salience or expected precision. In a placebo-controlled within-subject cross-over design, sixteen healthy human subjects performed a location-cueing task in which the proportion of validly and invalidly cued targets (percentage of cue validity, %CV) changed over time. Saccadic response speeds were used to estimate the parameters of a hierarchical Bayesian model. Behaviourally, galantamine led to a greater influence of probabilistic context (%CV) on response speed than placebo. Crucially, computational modelling suggested this effect was due to an increase in the rate of belief updating about cue validity (as opposed to the increased sensitivity of behavioural responses to those beliefs). Our results provide a new perspective on the effects of cholinergic neurotransmission on attentional processing by showing that cholinergic enhancement affects the computational mechanisms underlying attentional selection.
Dopamine and the cortical representation of reward
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The way humans behave is greatly affected by the principle expected utility, the combination of subjective value (SV) of the outcome of an act (is it rewarding?) and subjective probability (SP) of that outcome. In an initial study (n=42) we examined the electro-cortical representations of the anticipation of SV and SP during a cued Go/NoGo experiment. During this task cue letters signaled upcoming target letters to which participants had to respond. The probability of target letter appearance after the cue letter and the amount of money that could be won for correct and fast responses were orthogonally manipulated across four task blocks. Results show that reward availability affected a prefrontal reward P200 and a centro-parietal P300 ERP. Moreover, a fronto-central ERP was affected by both reward and probability manipulations. These results suggest that reward and probability are partially separately processed in the cortex. Furthermore, reward and probability information are integrated around 300 ms after presentation of the cue and possibly processed via a shared underlying cortical mechanism that may act to reduce uncertainty or to prepare for action. In a follow-up study we investigated the role of dopamine (and noradrenaline) in either of these processes by employing a within-subjects haloperidol/clonidine/placebo cross-over design (n=24) with the same cued Go/NoGo paradigm.

Trial registration
The Netherlands National Trial Register (NTR) (CC = 4493)
Optimizing the earliest memory stages: a role for acetylcholine and serotonin?

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Acetylcholine and serotonin both play an important role in encoding and consolidation of memories. However, it has also been suggested that these two neuromodulators take part, and might even interact, in processes initiated before conscious encoding even takes place. Sensory memory and novelty detection, two processes related to reduction of surprise, are part of those early stages. They can be measured with the mismatch negativity (MMN) and P3a components of the event-related potential, respectively. In a series of experiments, we examined whether cholinergic and serotonergic manipulations affect MMN and P3a components during a novelty oddball task. In this task, frequent standard stimuli were interspersed with infrequent deviant and infrequent novel stimuli at a pace of one stimulus presentation per second. Biperiden, a cholinergic agonist, and rivastigmine, a cholinesterase inhibitor, did not affect MMN amplitude. Acute tryptophan depletion, a method to reduce serotonin in the brain, and citalopram, a selective serotonin re-uptake inhibitor, were also unable to affect the MMN. No significant interactions between treatments were found related to the MMN. Cholinergic treatments did, however, affect the P3a amplitude: P3a was decreased after Biperiden intake and increased after Rivastigmine. The serotonergic manipulations did not affect P3a amplitude, neither were interactions found between treatments. Our results thus show that, although the cholinergic and serotonergic systems do not seem to play a role in sensory memory, acetylcholine’s role in novelty detection, and thus in handling surprise, is evident.
Processing of the mismatch negativity under the LSD state
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Background
Lysergic acid diethylamide (LSD) is a classic psychedelic drug and serotonin 2A receptor agonist. A common feature of the LSD state is its capability to provide an experience of modulating the salience of external events. The Mismatch Negativity (MMN) is an event-related potential/field (ERP/ERF), that indexes expectation disruption (or ‘surprise’) mechanisms, which have been shown to be modulated in patients with disorders of consciousness, as well as in schizophrenia and following ketamine administration. In this study the MMN paradigm was used to assess expectation and surprise mechanisms under LSD and placebo conditions in healthy participants.

Methods
A balanced order, within subject design was used for the study. 20 Healthy volunteers underwent MEG recordings following intravenous administration of LSD (75 mcg IV) and placebo at least 2 weeks apart. Participants were presented with auditory stimuli consisting of oddball and standard tones while resting inside the MEG scanner. Following preprocessing and averaging, the resulting event-related fields (ERF) were converted into scalp-map images and smoothed for statistical analysis corresponding to four conditions: auditory stimuli of standard tones under LSD (1) and placebo (2) and deviant tones under LSD (3) and placebo (4). The ERFs were entered into a within-subject analysis of variance with 2 main factors: ‘drug’ (LSD and placebo) and ‘expectation disruption’ (standard and deviant).

Results
An interaction effect between ‘expectation disruption’ and ‘drug’ factors was found in a right lateralized cluster in the scalp. Post hoc analyses within this ROI, reveal significant differences in the processing of standard tones between placebo and LSD conditions as well as deviant tones. Within the placebo condition the difference between standards and deviants was significant, while it wasn’t following LSD administration.
Conclusions
Results indicate a reduction of activity related to the processing of novel stimuli, while showing that the surprise response was increased under the LSD condition in large areas of the scalp for familiar stimuli. These findings may inform how salience mechanisms may be disrupted under LSD and is consistent with reports of “increased novelty” to familiar stimuli in the LSD state. Mechanisms underlying this modulation may be accounted by modulation of prediction error in the psychedelic state.

This research received financial and intellectual support from the Beckley Foundation and was conducted as part of a wider Beckley-Imperial research programme.
The effects of psilocybin on human EEG, comparison with animal models
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Objectives
Psilocin, the active metabolite of psilocybin, is a classical psychedelic tryptamine acting as an agonist at serotonin 5-HT2A/C and 5-HT1A receptors. It has been used extensively to model psychosis in humans as well as in animals, and during the last decade given more attention as a potential antidepressant and anxiolytic drug. Recent studies in healthy volunteers have shown that psilocybin leads to a global desynchronization of brain activity and disconnection of the main brain networks. The purpose of the current study is to compare the translational validity of psilocybin/psilocin effects on EEG activity and connectivity between healthy volunteers and rats.

Methods
For the human study, a 19 channel EEG of a standard 10/20 system was recorded with BioSDA09 amplifier (M&I). Subjects ($^1$M10/F10) were administered 0.26 mg/kg of psilocybin or placebo orally in a double-blinded, crossover manner. EEG was recorded before and at 50, 90, 180 and 240 min after drug administration. In the animal study, psilocin was administered to male Wistar rats ($n=10$) subcutaneously in dose of 4 mg/kg. Multichannel EEG with 12 cortical (6 homolateral pairs) electrodes at frontal, parietal and temporal regions were recorded for 10 min before and 90 min after dosing using BrainScope EADS 221 amplifier (M&I). EEG in animals was co-recorded with behavioural activity and epochs of inactivity were then subjected for further processing. Data was pre-processed using Brainvision and WaveFinder software followed by further power spectral and coherence analyses using Neuroguide software. Source localization of EEG activity was analysed by LORETA, 3D brain mapping in animals was performed using an in-house developed Matlab tool.

Results
Psilocybin induced an absolute as well as relative alpha power decrease in occipital regions, while beta and gamma power increases in frontotemporal areas in humans. The effects were most robust 50 min after drug administration. Source localization by LORETA confirmed the localization of EEG changes. However, it is of note that the gamma power cannot be distinguished from artificial motor activations. EEG coherence was mainly decreased in theta, alpha and beta bands, with some increases observed in beta and gamma bands. In rats there was a global power decrease in absolute power however relative power showed partly similar profile to humans with theta power decrease and
beta and gamma power increase. Furthermore, there was a global decrease of coherence in rats following drug administration.

Conclusions
The effects of psilocin/psilocybin resulted in similar direction of EEG changes in both humans and rats with disconnection (decreased coherence) being the most stable phenomenon observed, indicating good translational validity.

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Salvinorin-A induces a unique pattern of neurophysiological effects in humans characterized by alpha suppression and widespread increases in cortical delta activity
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Background
Salvinorin-A (SA) is a potent perception-modifying drug found in the leaves of the plant Salvia divinorum. Unlike 5-HT₂A agonists such as DMT, LSD and psilocybin, SA is a selective kappa-opioid receptor (KOR) agonist. Its pattern of effects in humans also shows important differences with that of the classical psychedelics. While subjects also experience intense visual and auditory phenomena, SA completely blocks external sensory perception, and leads to a characteristic total loss of contact with external reality. Here we investigated the neurophysiological correlates of SA effects in humans.

Methods
We measured spontaneous brain oscillations (EEG) in 24 healthy volunteers, before and after the administration of 1 mg vaporized SA. We recorded the EEG from 19 scalp leads and we calculated drug-induced energy changes in ten frequency bands between 1.3 and 40 Hz. Additionally, we computed the changes in the intracerebral current density distribution associated with the voltage values recorded at the scalp.

Results
SA administration led to rapid and significant changes in brain oscillations that coincided with maximum drug levels in plasma. SA suppressed the alpha rhythm (7.5-13 Hz) and markedly increased slow delta activity (1.3-3.5 Hz). Less prominent effects included increases in the theta (3.5-7.5 Hz) and low gamma (35-40 Hz) bands. Alpha decreases were localized over parieto-occipital regions, including the posterior cingulate cortex and visual areas. Delta increases were observed over most of the brain, with the maximum located over auditory and visual cortex in the left temporal lobe. Theta increases were found over left temporal and frontal areas. Finally, gamma increases were restricted to visual areas in the occipital cortex.

Conclusion These results show a unique pattern of neurophysiological effects for SA in humans. While it shares with serotonergic psychedelics the alpha-suppressing action, its main neurophysiological signature is an atypical enhancement of slow delta activity. These differences may explain the marked differences in subjective effects between SA and 5-HT₂A agonists.

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QEEG signatures predicting antidepressant response to ketamine

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Objective
Treatment-resistant depression (TRD) is a disabling disorder that negatively impact patient’s morbidity and mortality and constitutes a major challenge for current psychopharmacology. The discovery of rapid-acting antidepressive action of ketamine has motivated studies aiming to reveal the molecular mechanism of this effect and to enable the clinical application of similarly rapid-acting antidepressants. In our two studies, the time-course of effects of ketamine was assessed in treatment-resistant depressive patients by QEEG to elucidate changes associated with treatment effect and to assess potential predictors of treatment response.

Methods: The pool analysis was completed from data of two double-blind, cross-over, placebo-controlled studies, assessing the effect of single infusion of ketamine (0.54 mg/kg within 30min) in altogether 50 inpatients with major depressive disorder: EEG data were analysed during the infusion (10min and 30min) and 24hours after ketamine administration using exact low-resolution electromagnetic tomography (eLORETA). Response to treatment was defined as a ≥50% reduction of MADRS score.

Results
Ketamine induced immediate (10min and 30min) decrease of parietooccipital sources of alpha-1 and alpha-2 activities and an increase of gamma-sources in all subjects. Responders to medication were characterized by excess of mediofrontal delta and theta sources in comparison to non-responders. Moreover, only the responders showed significant changes that persisted 24 hours after infusion, while no significant changes were observed in non-responders. Among the clinical variables we have found a significant correlation between the BPRS score during ketamine infusion and MADRS score at day 7, and the intensity of psychotomimetic symptoms during infusion seems to be the strongest clinical predictor of antidepressive effect of ketamine. Regarding the QEEG parameters, the patients with better responses showed higher pre-treatment theta activity in mediofrontal areas and in the rostral anterior cingulate. Better response to ketamine was also connected with higher pre-treatment lagged phase synchronization (i.e. higher connectivity) between anterior cingulate and mediofrontal cortex at theta and alpha-1 frequency bands.
Conclusion

Our results suggest that an acute increase of mediofrontal cortical sources of theta and delta activities after ketamine infusion could be potential biomarkers to differentiate responders and non-responders to ketamine. Higher pre-treatment theta activity in mediofrontal areas together with higher lagged phase synchronization between anterior cingulate and mediofrontal cortex at theta and alpha-1 frequency bands could serve as predictors of treatment response to ketamine. Moreover, the antidepressive effect of ketamine seems to be undoubtedly connected with patient’s psychotomimetic experience.

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Oral presentations
Nonlinearity of the visual system assessed by cross-frequency phase coupling
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Background
Processing of visual input by the brain is a highly nonlinear operation, involving complex interactions among neuronal networks. Nonlinear visual system activity includes harmonic interactions, thought to reflect resonance of neural processing, whereas intermodulation, being the contribution of multiple input frequencies to one output frequency, relates to functional integration [1]. Using a sum-of-sinusoid signal as visual input [2], it is possible to elicit a richer class of nonlinear responses than the classic pulse train stimulus, thereby providing a more complete description of nonlinearity. Here, we will use nonlinear EEG analyses to quantify higher-order nonlinearities in visual processing.

Methods
Ten healthy participants were subjected to bi-sinusoidal light stimulation of 13 and 23 Hz for 320 1s-epochs, while scalp EEG (8 electrodes) was recorded at the occipital, parietal and frontal lobes. The frequencies of light stimulus were chosen to guarantee no overlap of their harmonic and intermodulation frequencies for different orders of nonlinearity. Nonlinear interactions and time delay from stimulus to cortex were analyzed in the frequency domain using novel phase synchronization measures [3] and amplitude spectrum.

Results
Higher harmonic and intermodulation interactions were detected between visual input and cortical responses. First to fourth order phase coupling interactions were enhanced in the visual cortex compared to parietal and frontal responses. Spectral amplitude differences were less pronounced between cortical regions. Time delay estimation showed a delay between light stimulus and visual cortex of 118±21 ms, significantly higher than the delay between stimulus and frontal or parietal lobes.

Discussion
This study demonstrates the potential of using sum-of-sinusoid light stimulation and quantitative nonlinear EEG analysis to identify higher-order nonlinear dynamics of visual processing. We foresee that application of the described frequency interaction analyses
can further our insight in the nonlinear dynamics of visual processing not only in healthy subjects, but also with respect to the pathophysiology of neurological diseases with visual manifestations that relate to cortical hyperexcitability, like migraine and epilepsy.

References
Whole-brain time-frequency analysis of event-related potentials for the assessment of pharmacodynamic effects in the human brain
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We are developing Whole Brain Time-Frequency (WBTF) analysis as a new physiological biomarker for clinical trials of pharmacodynamics of novel drugs. WBTF analysis expands the power of event-related potential (ERP) assessment by using wavelets to measure both evoked (phase-locked) and induced (non-phase-locked) activity. Unlike traditional ERP measures, which are indexed by specific electrodes and peak latencies, WBTF analysis measures integrated change in brain responses across time, frequency and space to infer whether a drug has a significant effect. WBTF analysis also uses permutation tests and multiple comparison corrections to identify important within-subject changes between conditions and rule out differences arising from recording noise, artifacts or random variability.

The specific aim of this study was to assess the sensitivity and specificity of WBTF analysis to drug effects that are typically measured with ERP amplitudes and latencies. We simulated effects of dose-related changes in N1-P2-P3 ERP components and 40-Hz induced gamma bursts at 24 electrodes. Simulations included a range of amplitude effects, latency effects and signal-to-noise ratios, serving to define the sensitivity and specificity of WBTF analysis to ERP differences.

The simulations allowed us to optimize parameters for WBTF analysis, including choice of analyzing wavelets, energy normalization, baseline correction, measures of evoked and induced activity, and method of testing significant differences. We found that WBTF analysis reliably detects small differences in evoked activity (on the order of 10%) in realistic noise and background EEG conditions. We found similar detectability of small differences in induced 40-Hz gamma bursts.

It is the goal of the further studies to investigate the clinical relevance of these observed differences using WBTF analysis, and to relate the evoked and induced components ERP differences to mechanisms of drug action. Currently we are applying WBTF analysis to data from three Phase 1 clinical trials of novel compounds for schizophrenia in both healthy controls and schizophrenia patients.
Dysregulation of hyperpolarization-activated inward cation current \( (I_h) \) affects thalamocortical oscillations: the role of the auxiliary subunit TRIP8b on HCN channel function in thalamic and cortical neurons.

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Background

The family of hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels consisting of four different isoforms (HCN1-4) have a major role in controlling neuronal excitability and generation of rhythmic oscillatory activity in individual neurons and neuronal networks [1, 2]. These channels activate in response to hyperpolarizing potentials negative to -50 to -60 mV and depolarize the resting membrane potential. HCN channels are regulated by small molecules like cyclic nucleotides and different accessory proteins. TRIP8b is a brain-specific accessory subunit of HCN channels which controls the gating, surface expression and trafficking of different HCN channels subunits in many regions of brain [3-5]. The role of this protein for \( I_h \) characteristics in thalamic and cortical neurons and the functional consequences of TRIP8b dysregulation for thalamocortical oscillations however is not yet fully understood. The present study aimed at providing a better understanding of the functional role of TRIP8b in the thalamocortical system and shedding some light on possible dysfunctional aspects by combining in vitro and in vivo electrophysiological approaches.

In this study, \( I_h \) was measured in whole cell patch clamp recordings from thalamocortical (TC) neurons of different thalamic nuclei, as well as pyramidal neurons in layer V and VI of the somatosensory cortex of TRIP8b-deficient (TRIP8b⁻/⁻) and control (C57Bl/6) mice (p15 – p90). Effects of TRIP8b-dependent dysregulation of \( I_h \) on thalamocortical oscillations was monitored by local field potential (LFP) recordings from the ventral-posterior medial complex of the thalamus (VPM) and somatosensory cortex (p 90 – p120), regions which are known to be involved in generation of normal and also pathological thalamocortical oscillations.

Results

Characterization of \( I_h \) in the thalamocortical system in the absence of the auxiliary subunit TRIP8b showed a significant decrease in \( I_h \) density and changes in intrinsic properties and firing patterns of TC and cortical pyramidal neurons. These changes were accompanied by an increase in cAMP sensitivity in TC neurons. Dysregulation of \( I_h \) in the thalamocortical system of TRIP8b⁻/⁻ mice was associated with altered thalamocortical oscillations revealing a significant increase in slow oscillations in the delta frequency range (0.5-4 Hz) during episodes of active-wakefulness.
Conclusion
The results of our study point to the importance of TRIP8b, as a brain-specific auxiliary subunit of HCN channels, in regulation of cell and network oscillations. It was demonstrated here that the presence of TRIP8b is necessary for modulation of thalamocortical delta oscillations due to its direct effect on HCN channels protein expression in the thalamocortical system.

References
Advanced EEG imaging of neuronal network interactions during spatial working memory performance in rats: paving the road for pharmacological assessments

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Cognitive processes are based on the coordination of interactions of populations of neurons that are distributed within and across different specialized brain areas. Accumulating evidence suggests that neuronal oscillations play a pivotal role in driving brain communication. This communication is affected in many neurodegenerative diseases. Accordingly, understanding network interactions during cognitive activity is crucial for a better comprehension of neurodegenerative consequences for cognitive functioning as well as for assessing the efficacy of novel pharmacological treatments. The purpose of the present study was to evaluate putative EEG-based biomarkers during the trial-unique delayed nonmatching-to-location (TUNL) task in rats. The task assesses memory for location across different delays and spatial separations in a computer-automated touchscreen set-up. Once EEG-instrumented rats reached performance criteria (80% accuracy in an 8 sec delay for two consecutive days), brain activity in the CA1 region of the hippocampus, medial prefrontal cortex, and retrosplenial cortex was monitored during two consecutive TUNL sessions using an 8 sec and a 16 sec delay. Time frequency-based analysis of EEG readouts was used to investigate neuronal connectivity during the different delays comparing correct vs. incorrect trials. In particular, cross-frequency coupling (CFC, when the phase of a low frequency oscillation drives the amplitude of the coupled higher frequency oscillation) was analyzed as this has been suggested a possible mechanism facilitating working memory. It was hypothesized that functional connectivity during the delay will be reduced during incorrect trials compared to correct ones for both delays and separations. Behavioral results confirmed that accuracy was higher in the larger separation for the 8 sec delay ($M = 84.29\%$, 95%–CI [81.03, 87.55]) compared with smaller separation for the same delay ($M = 74.99\%$, 95%–CI [69.89, 80.09]). Furthermore, the 16 sec appeared to be more challenging as accuracy was reduced for both large ($M = 63.05\%$, 95%–CI [55.95, 70.15]) and small separation ($M = 60.41\%$, 95%–CI [55.57, 65.25]) compared with the 8 sec delay. Interestingly, results from the CFC during the delay support our hypothesis as 8 Hz frequency modulation of 90 Hz amplitude in the medial prefrontal cortex showed a more rapid decrease in CFC during the delay for the incorrect trials in both delays and separations compared to the correct trials. Overall, results identified the critical role of neuronal oscillations and connectivity for working memory in the TUNL task. This study reinforces the strength of combining multiple approaches to further understand cognitive processes and assessment of pharmacological treatments.
EEG functional connectivity of Brodmann area 24 in obsessive-compulsive disorder

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Background
A growing body of evidence have challenged the traditional orbitofrontostriatal hypothesis and suggested that dysregulation of widespread brain networks may underlie the OCD disorder. In last decades, the increasing attention of neuroscience research has been payed to large-scale network organization of the brain. Three prominent networks were identified: “Central Executive Network”, “Default Mode Network” and “Salience Network”, responsible for synchronization of anticorrelated activity of DMN and CEN. Several studies have stressed the role of the dorsal anterior cingulate cortex, a core structure within the salience network, in OCD pathophysiology. Our two previous studies also revealed abnormal EEG activity in this structure (Brodmann area, BA 24), however little is known about its EEG functional connectivity in OCD. Based on our previous findings, we tested functional connectivity between EEG sources in BA 24 and rest of the brain in the group of OCD patients and in healthy controls.

Methods
96 in-patients diagnosed with OCD and 95 healthy controls matched for age and sex were included in the study. All subjects were right-handed. 27 OCD patients were drug-free and 69 were medicated with SSRIs. All subjects underwent 19-channel resting-state EEG examination. Functional connectivity was analysed in LORETA-KEY software. We assessed connectivity between centroid of BA 24 and centroids of all the other Brodmann areas as defined in the LORETA-KEY software. Lagged nonlinear connectivity was computed in eight frequency bands: delta (1.5 - 6 Hz), theta (6.5 - 8 Hz), alpha 1 (8.5 - 10 Hz), alpha 2 (10.5 - 12 Hz), beta1 (12.5 - 18 Hz), beta 2 (18.5 - 21 Hz), beta 3 (21.5 - 30 Hz) and gamma (30.5 - 44.0 Hz). Groups were compared using t-statistics and permutation testing to correct for multiple comparisons.

Results
Drug-free and SSRIs medicated patients did not differ from each other in functional connectivity and therefore they were further tested as a unitary group. Compared with controls, OCD patients had higher lagged nonlinear functional connectivity between BA 24 and BA 5 and BA 7 in the beta 3 as well as in the gamma frequency band (p<0.05). In the gamma band the results were significant only for the left BA 5 and 7, however connectivities in the right hemisphere were close to threshold.

Conclusion
We hypothesize that an aberrant synchronization between default mode and central executive network related to the aberrant activity of the salience network may underlie symptoms of OCD.

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Cortical network reorganization in mild and prodromal Alzheimer disease: graph theory approach on resting state EEG recordings
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Background
Alzheimer’s disease (AD) has a long preclinical period in the absence of overt symptoms in which the process progresses until it crosses a threshold to clinically recognizable dysfunction [1]. Graph theoretical analysis of cerebral networks has been implemented in AD challenging the classical concept of neurological disorders being either ‘local’ or ‘global’, and have pointed to the overload and failure of hubs as a possible final common pathway in neurological disorders. Previous EEG studies on the comparison between AD and control subjects reported divergent results [2]. An intermediate trend was found in subjects with mild cognitive impairment (MCI) with respect to AD and control subjects [3]. The aim of the study was to assess by means of graph theory analysis if AD patients with mild dementia could show a different cortical organization from age matched control subjects and if these possible differences could be already present at the stage of MCI.

Results
The main finding of the present study is that network reorganization is evident in AD since the prodromal stage (AD-MCI). Specifically, AD-MCI and AD showed a lower number of links among nodes than control group (p=0.0007). Both inward and outward links among nodes and brain areas with a high level of functional connectivity (so-called hubs) were found to be reduced in both AD-MCI and AD patients. Hubs in the parietal areas (P3, P4, and Pz) showed lower number of links in AD-MCI and AD than control group. Temporal nodes showed lower clustering coefficient and local efficiency in patients than control group. Significant differences between AD-MCI and AD were found in the right occipital node. Indeed, the clustering coefficient and the local efficiency was reduced in AD compared with AD-MCI in O2 (p<0.05).

Conclusions
Our results suggest that brain network functional alterations mainly involved the temporal nodes in prodromal stage of AD, whereas brain dynamic changed in the posterior areas with disease progression to overt AD dementia.

The functional disconnection between temporal and parieto-occipital areas could be related to medial temporal lobe atrophy which is a characteristic neuropathological change in the early stage of AD [4].
References


Sleep disturbances in obsessive-compulsive disorder: Association with response to repetitive transcranial magnetic stimulation (rTMS)
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Background
Obsessive-compulsive disorder (OCD) is a debilitating disorder with a substantial portion of patients not responding to first-line treatment. Repetitive transcranial magnetic stimulation (rTMS) is an effective augmentation strategy for treatment-refractory patients, but as the response rate is approximately 35% [1], it is important to identify predictors of rTMS response. Emerging evidence indicates a relatively high prevalence of sleep disturbances in OCD patients, in particular circadian rhythm sleep disorder (CRSD) [2]. It is therefore proposed that sleep disturbances may affect treatment efficacy.

Methods
In this open-label study, 22 OCD patients received at least 10 sessions of rTMS treatment targeted at the supplementary motor area combined with psychotherapy. They were compared to a matched control group of healthy subjects to examine sleep disturbance. Treatment outcome was measured by monitoring obsessive-compulsive as well as depressive symptoms each fifth session using the YBOCS and BDI, respectively. Treatment response was defined as a reduction > 35% on the YBOCS. Sleep disturbances were measured by means of self-report (PSQI, HSDQ) and actigraphy. Treatment response prediction models were based on subjective and objective measures of CRSD and insomnia.

Results
OCD patients showed a higher rate of sleep disturbances than controls. The OCD group consisted of 12 responders and 10 non-responders. Responders showed a significantly larger reduction in both obsessive-compulsive and depressive symptoms, while no difference in baseline severity existed. Sleep disturbances, on the contrary, were more severe in non-responders than responders. Furthermore, a predictive model based on CRSD could accurately predict treatment response with 83% sensitivity and 63% specificity, whereas the insomnia model could not.
Conclusions
Sleep disturbances in OCD can significantly predict rTMS treatment response, in particular CRSD. Therefore, CRSD may serve as a biomarker for different subtypes of OCD that correspond with response to specific treatment approaches.

Competing interests
PBF is supported by a NHMRC Practitioner Fellowship (1078567).
PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Cervel Neurotech and Brainsway Ltd and funding for research from Neuronetics and Cervel Neurotech. He is on the scientific advisory board for Bionomics Ltd. MA reports research grants, options/shares from Brain Resource Ltd. (Sydney, Australia) and neuroCare group and he is also a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents.

References
Glutamatergic deficit and negative symptoms: new evidence from the ketamine model of schizophrenia

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Targeting the N-methyl-D-aspartate-receptor (NMDAR) is a major approach for treating negative symptoms of schizophrenia. The ketamine model of schizophrenia has the advantage of comprehensively producing schizophrenia like symptoms such as positive, cognitive and negative symptoms in healthy volunteers. The amplitude of the Mismatch Negativity (MMN), a neurophysiological parameter related to infrequent stimuli, is known to be significantly reduced in schizophrenic patients but also in healthy controls receiving ketamine [1,2]. Accordingly, it was the aim of the present study to investigate whether changes of MMN during ketamine administration are related to the emergence of negative symptoms in healthy subjects.

Therefore, we examined the impact of ketamine on MMN amplitudes and its sources (sources localization approach: low resolution electromagnetic tomography (LORETA)) by means of 64-channel electroencephalography (EEG) recording during performance of an auditory MMN paradigm and assessed the psychopathological status using the Altered State of Consciousness (5D-ASC) Rating Scale and the Positive and Negative Syndrome Scale (PANSS). Twenty-four male, healthy volunteers were measured with pharmacological EEG using a single-blind, randomized, placebo-controlled crossover design.

We identified significant changes of the MMN response, to both duration and frequency deviants, under ketamine condition as well as a significant increase in all PANSS scores. Reductions of MMN amplitudes were significantly correlated with more pronounced negative symptoms, assessed by the PANSS.

Accordingly, the MMN might represent a biomarker for negative symptoms in schizophrenia related to an insufficient NMDAR system and could be used to identify schizophrenia patients with negative symptoms due to NMDAR dysfunction and thus to determine a maximal benefit of drugs modulating neurotransmission at the NMDAR.

Competing interests
The authors declare that they have no competing interests.

References
Isolated epileptiform discharges in psychiatry: outcomes in an integrative practice
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Background
The search for biomarkers that can inform medication decisions in neuropsychiatric disorders is a goal of the Research Domain Criteria project under the National Institute of Mental Health. Isolated epileptiform discharges (IEDs) may be such a biomarker. IEDs have been linked to increased psychopathology that traverses many diagnoses [1]. It has been suggested that IEDs may represent an epiphenomenon with an etiology of unappreciated significance [2]. The literature suggests that anticonvulsants should be considered when IEDs are identified [3,4]; however, outcome studies have yet to be published. This study investigates the predictive value of IEDs as a biomarker for the use of anticonvulsants on a large cohort of patients.

Method
We reviewed refractory cases from a large multidisciplinary practice whose EEG readings contained IEDs and were subsequently medicated with anticonvulsants by the clinic’s psychiatrist. The psychiatrist’s follow up progress notes were assessed to determine the impact of adding anticonvulsants. Ratings were based on clinical presentation and reported in three categories: Improved, unchanged, and more severe. There were two exclusion criteria: a prior diagnosis of seizure disorder and a history of prior treatment with anticonvulsants. Of the 735 patients in our database, 325 (44.22%) were identified with IEDs. The final sample was comprised of 76 refractory cases. The study included 61 males (80.26%) and 15 females (19.74%) ages 5 to 52.

Results
Of the 76 cases treated with anticonvulsants, the vast majority were found to be improved in follow-up progress notes: Improved 65 (85.53%), Unchanged 6 (7.89%), and More Severe 5 (6.58%).
Conclusions
IEDs predict positive treatment outcome to anticonvulsant medication and may not only represent a biomarker for medication selection but also a step towards an evidence-based diagnosis. This review serves as the first large outcome study in which patients with IEDs were treated with anticonvulsants. Our findings suggest that EEG screening should be utilized in all refractory cases regardless of age, gender, or diagnosis. When IEDs are identified, anticonvulsants should be considered as a treatment option.

Consent to publish
This study does not contain details relating to individual participants.

Competing interests
The authors declare that they have no competing interests.

References
Do cannabinoid antagonists affect cognition?

SLV326 induces changes in theta and gamma bands in active rats

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Cannabinoid CB1 antagonists have been investigated for possible treatment of e.g. obesity-related disorders. However, clinical application was halted due to their symptoms of anxiety and depression. In addition to these adverse effects, we have shown earlier that chronic treatment with the CB1 antagonist rimonabant may induce convulsive seizures which were EEG-confirmed. However, due to the wide distribution of CB1 receptors throughout the CNS, it is highly unlikely that chronic blocking of the CB1 receptor is only manifested in seizures. CB1 agonists have been described to alter the EEG frequency spectrum. No such data are available for CB antagonists.

In a regulatory repeat-dose toxicity study “muscle spasms” were observed in Wistar rats, daily dosed with the CB1 receptor antagonist SLV326 during 5 months. In selected SLV326-treated and control animals, EEG and behavior were monitored for 24 hours. Subsequently, random segments of the interictal EEG were selected, totaling 20 minutes per animal. These segments were assigned to subsets of ‘active state’ or ‘passive state’, based on Passive Infrared (PIR) motion detection. Spectral information was calculated using a Fast Fourier Transformation analysis.

25% of SLV326 treated animals showed, EEG-confirmed, spontaneously occurring generalized convulsive seizures, whereas all controls were seizure-free. The behavioral signs of the seizures were typical for a limbic origin.

The frequency spectrum of the interictal EEG of the treated rats showed a lower theta peak frequency, as well as lower gamma power compared to the controls. These frequency changes were state-dependent: they were only found during high locomotor activity. However, the treatment did not affect the amount of locomotor activity itself.

Apart from confirming our previous finding that long-term blockade of the endogenous cannabinoid system can provoke limbic seizures in otherwise healthy rats, this study shows that SLV326 alters the frequency spectrum of the EEG, but only when rats are highly active. It is therefore likely that the EEG effects caused by SLV326 are linked to higher order behavior that might be present during locomotion. Theta rhythm is shown to be a marker of complex behavior; and gamma rhythm is typically associated with cognitive functions. Therefore, these observations suggest that CB antagonists might have effects on complex behavior and cognition.
EEG connectivity on sources in male non-smokers after nicotine administration during resting-state
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Background
New developments in pharmacology are based on non-invasive neuroimaging, particularly by leveraging and optimizing techniques and methodologies already validated in basic neuroscience. Particularly interesting is the use of connectivity measures of electromagnetic oscillatory activity regarding the modulation of vigilance. Indeed, several recent anesthesiology papers found a connection between vigilance and the connectivity measured from electromagnetic oscillatory activity[1]. We present an EEG connectivity study aimed to establish whether nicotine-induced modulations of vigilance impact connectivity.

Methods
EEG activity was recorded in an eyes-open and eyes-closed condition before and after drug administration in thirty healthy male non-smokers. The subjects were randomly allocated either to a nicotine group (14 subjects, 7 mg transdermal nicotine) or to a placebo group. A double-blind placebo-controlled design was implemented. With source reconstruction procedure (eLORETA algorithm), we extracted thirteen time-series representing thirteen regions of interest (ROIs). Each ROI was anatomically precise and belonged to the resting-state network which seems to be modulated specifically by eyes-open and eyes-closed activity. In the literature such resting-state network is labeled as the Default Mode Network. Here we conducted connectivity analysis (renormalized Partial Directed Coherence, rPDC) on the ROIs’ time-series, focusing on the frequency range of 8.5 to 18.4 Hz. Such frequency range was further subdivided into three frequency bands (α1, α2 and β1) in order to comply with current EEG standards of practice.

Results
Our connectivity analysis found that during eyes-closed, nicotine decreased feed-back connectivity (from precentral gyrus to precuneus, angular gyrus, cuneus and superior occipital gyrus) at 10.5-12.4 Hz (α2). During eyes-open, no significant results were found at any frequency range.
Conclusions
We interpreted the results by help of previous anesthesiology literature about an anti-correlated relationship between feed-back and feed-forward connectivity. Such relationship emerged by pharmacologically-induced sedation during eyes-closed condition. Our results suggest that nicotine potentially increases the level of vigilance. Such nicotine-effect is particularly prominent during the eyes-closed condition.

Competing interests
Nothing to declare

References
Inhaling noble gas xenon in sub-narcotic dose: impact on emotion and EEG dynamics in healthy volunteers
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Background
N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine, have rapid antidepressant effects in patients with Major Depression Disorder (MDD). Given the similar mechanisms of action, an inhalational general anesthetic Xe performs its neuroprotective functions through binding to glycine site of glutamatergic NMDA receptor competitively and blocking it. We hypothesized that Xe being inhaled in sub-narcotic doses, may induce positive affect, thereby manifesting its translational potential as putative antidepressant.

Methods: In placebo-controlled, double-blind study 13 healthy volunteers were randomly assigned to 15 min inhalation session either an admixture of up to a maximum of 25% Xe/30% oxygen/45% nitrogen (“active treatment”) or 70% nitrogen/30% oxygen (“placebo control”) for 15 min. The inspiratory Xe concentration was titrated during the first 5 min until 25% was achieved. Peak concentrations were maintained for 5 min. The primary endpoints were the changes on the emotional 100 mm visual analog scales (VAS) and EEG individual alpha frequency (IAF), i.e., neurophysiological endophenotype reportedly associated with MDD treatment sensitivity [1]. The research received approval of the institutional ethics committee.

Results
No adverse events occurred. Three participants withdrew after the first session, leaving an evaluable population of 10 subjects who received both treatments. The 3-way ANOVA of VAS scores with the factors of Gas (2: Xe, N) Time (2: Baseline, 10 min after inhalation completion) Emotion (10 discrete emotions) where the first factor was independent and two remaining were repeated measure yielded significant interactions Gas Time (F(1,8)=10.92, p<0.001) and Gas Time Emotion interactions (F(9,72)=8.51, p=0.003).
Fig 1. Intensity of experienced discrete emotions at baseline and post-inhalation period for Xenon (Xe, “active treatment”) and nitrogen (N, “placebo”) conditions.

Analysis of common means of these interactions along with separate 2-way Time (2) ´ Emotion (10) ANOVAs for each gas condition specified that Xe (Time ´ Emotion - F (9,72)=7.91, pG-G=0.001) vs. N (Time ´ Emotion - F (9,72)=2.58, pG-G=0.142) selectively enhanced positive emotional experience involving surprise, joy, happiness, owe, and bliss (planned comparisons significance range from p=.012 to p=.036). And as an additional point Xe weakened intensity of sadness experience (p=0.034). As for EEG dynamics the 2-way ANOVA (Gas 2: Xe, N ´ Time 3: Baseline, Inhalation and Post-Inhalation periods) indexed that Xe rather than N modulated IAF. According to the interaction Gas ´ Time (F(2,18)=4.24, p=0.043) and subsequent post-hoc analyses, inhaling Xe significantly decreased IAF whereas at 10th min after the completion of inhalation session it returned to the baseline level (IAF higher at both baseline and post-inhalation periods vs Xe-inhalation condition - p=0.02 and p=0.03 respectively). Effects of the nitrogen were insignificant.

Conclusions
The findings evidence that Xe, devoid of ketamine’s toxicity issues, may have marked mood enhancing effects in healthy volunteers. This effect is accompanied by transient EEG IAF down-regulation. Subsequent placebo controlled clinical studies are required to tackle a putative antidepressant potential of this gas.

References
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Poster presentations
Modulation of the NMDA receptor function enhances hippocampal network oscillations, connectivity and synaptic LTP in-vivo: A case study with a Glycine Transporter-1 Inhibitor
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Hypofunction of N-methyl-d-aspartate receptors (NMDARs) has been associated with deficits in synaptic plasticity and cognitive decline as found in neuropsychiatric and neurodegenerative disorders such as Alzheimer’s disease. Glycine and D-serine are endogenous ligands of the NMDAR and therapeutic approaches that enhance NMDAR activity through increases in glycine and/or D-serine levels are expected to enhance synaptic strength and to potentially improve have impact on cognition processes.

The present in-vivo study investigated whether positive modulation of brain glycine levels, through modulation by the glycine transporter 1 (GlyT1) inhibitor SSR504734, affects network connectivity and long-term potentiation (LTP) at the hippocampus. For in-vivo network oscillations and connectivity, multichannel EEG recordings were performed in conscious Sprague-Dawley rats from frontal cortical, hippocampal CA1 and CA3 and dentate gyrus (DG) structures after subcutaneous administration of vehicle or SSR504734 (2.5, 10 and 40 mg/kg). For hippocampal synaptic plasticity, rats were anesthetized with urethane and recording and stimulating electrodes were inserted at the DG and at the medial perforant pathway (MPP), respectively. Population spike (PS) amplitudes (PSA) and excitatory postsynaptic potential (EPSP) slope were measured before and 2-hrs after high-frequency stimulation (HFS).

SSR504734 (at 40 mg/kg) elicited robust EEG slow theta oscillations (4-6.5 Hz) at the DG, CA1 and CA3 and in addition slow gamma oscillations (30-50Hz) in the frontal areas, next to network coherence changes between frontal and CA1 recording sites, which were dissociated from motor behavior. SSR504734 (at 40 mg/kg) enhanced LTP of the PS amplitude after HFS of the MPP synapse, whereas the potentiation of EPSP slope was short-lived.

The present data support the hypothesis on a facilitating role of the NMDARs glycine binding site on network oscillations and synaptic efficacy at the medial perforant path of the DG. Future studies will evaluate novel approaches targeting D-Serine modulatory sites, for example by inhibition of the enzyme d-amino acid oxidase (DAAO), which slows the break-down of D-serine, or by its transporter; the alanine-serine-cysteine-1 (Asc-1), the abnormal glio-transmission of which has been linked to synaptic failure in Alzheimer’s disease.
Pharmaco-EEG study of combination anticonvulsant and antioxidant in treating pharmacoresistant focal symptomatic epilepsy (clinical-experimental study)

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Background
Up to 40% of epilepsy patients remain resistant to drug therapy. A way to increasing effectiveness and reducing side effects of anticonvulsants is their combination with antioxidant. The hypothalamus is main pathogenic determinant structure for influence of valproic acid drugs. Purpose of this work is study the possibility of applying combination of Depakine Chronosphere granules of prolonged action and antioxidant from group of 3-oxypiridin Mexidol in the treatment of pharmacoresistant symptomatic focal epilepsy.

Materials and methods
In rats with chronic cobalt epileptogenic lesion we implanted long-term electrodes to motor cortex, dorsally section of hippocampus and lateral nucleus of hypothalamus. In subcortical structures the electrodes were implanted using stereotaxic device [1].

64 patients with pharmacoresistant focal symptomatic epilepsy were examined. Pharmaco-EEG study of patients was conducted. 1 group - 33 patients received Depakine Chronosphere; 2 group 31 patient combinations of Depakine Chronosphere and Mexidol. Computer analysis of the EEG with program “BRAINSYS[2].

Results
Depakine Chronosphere in rats with cobalt-induced epilepsy reduces number of epileptiform discharges in cortex electrogram (5times), hypothalamus (3,2) and hippocampus (3,9 times). Depakine Chronosphere completely eliminates tonic-clonic seizures among all animals.

The optimal individual dose of Depakine Chronosphere was confirmed in patients by determination of drug concentrations in serum and by pharmaco-EEG. On the 15 day on background of half optimal dose of Depakine Chronosphere, we inject Mexidol (200mg) and in 40 minutes pharmaco-EEG study were conducted. On the 16th day Mexidol was administered 4 hours after. Statistical analysis 1 and 2 group revealed reliable difference. After combined treatment complete control was achieved in more patients (43.75%) and 50%-control (56,25%). After 1 month combined course we got normalization of pharmaco-EEG parameters.

Conclusion
Antioxidant Mexidol enhance the anticonvulsant effect of Depakine Chronosphere. Pharmaco-EEG studies showed the optimal effectiveness of the interval between them in 4 hours.

References
Neurofeedback training as a treatment for dyslexia
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Dyslexia is amongst the commonest of neurobiological disorders, affecting about 20% of children in Norway. Its heterogeneity makes it difficult to establish a single treatment which is suitable for most of the affected. According to the phonological theory of dyslexia, the disorder is caused by a deficit in the representation, storage and recall of speech sounds. Different brain areas have been linked to the phonological deficit by means of different brain imaging techniques, among other quantitative electroencephalography (qEEG).

The aim of this study was to improve reading ability in children with dyslexia by means of individualized neurofeedback training. The study was conducted as a pre-post intervention single-subject design with 5 participants, aged from 13 to 14 years. The intervention consisted of 25 sessions of neurofeedback training, 15 beta/theta frontocentral sessions and 10 individualized sessions, mostly towards the language areas. The effect of the intervention was measured by means of qEEG and the LOGOS (a Norwegian dyslexia assessment battery).

The results showed improvement in reading abilities and phonological skills amongst all participants. Furthermore, qEEG analysis showed increased alpha activity in several brain areas, and normalization of theta and beta activity in comparison to a normative database. An increase of alpha activity may possibly indicate changes in alpha coherence which can be an indication of improved attentional processes. This may explain the improvements in reading and phonological skills. The analysis also confirms the heterogeneity of dyslexia, and the complicity of several brain areas that are involved in dyslexia.

This study is limited by the small number of participants, and the restriction in time (the number of training sessions offered). However, the improvement in reading and phonological skills in this study suggests that neurofeedback training may be an effective and relevant intervention for adolescents with dyslexia. But, further research in this area with larger samples and a larger number of training sessions is required.

The study was approved by the regional ethics committee.

Competing interests
There are no competing interests.
Mismatch negativity (MMN) in serotonergic model of psychosis induced by psilocybin
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Background
The auditory MMN (mismatch negativity) is considered to be an index of automatic context-dependent information processing and auditory sensory memory. MMN deficit is a characteristic endophenotype of schizophrenia. A 5-HT2A agonist psilocybin induces acute transient psychotic symptoms and is extensively used as a putative pharmacological model of schizophrenia. Our aim was to investigate the effect of psilocybin on this pre-attentive cognitive functions.

Methods
A double-blind, placebo controlled study design was used. 20 healthy adult volunteers were administered a dose of psilocybin (0.26 mg/kg) and placebo per os in 2 separate sessions. Auditory MMN was recorded in sound and electrically shielded room, 120 minutes after ingestion of psilocybin/placebo. Participants were lying down with their eyes closed in a comfortable setting with two sitters who were present during whole experiment.

MMN
A single deviant paradigm with 1350 standard (1000Hz, 75dB SPL, 100ms duration) and 75 deviant in frequency (1200Hz, 75dB SPL, 100ms) tones were presented binaurally in regular order when every 20th was deviant tone. Data was acquired with a standard 32-channel digital EEG amplifier BrainScope (unimedis, Prague) with 21 Ag/AgCl scalp electrodes placed according to the 10/20 system and sampled at 1000 Hz.

Results
Mismatch negativity was calculated by subtracting the average of frequently occurring stimuli from the average of deviants. There were no significant differences in latency, absolute amplitude and area under curve of MMN during psilocybin intoxication compared to placebo. Furthermore, there were no correlations between subjective effects induced by psilocybin (HRS and ASCS) and MMN.
Conclusion
Our results correspond with previous findings [1]. Psilocybin does not affect processing at the level of pre-attentive cognition and the auditory sensory memory. This effect is probably due to different underlying receptor mechanism as the generation of MMN is strongly dependent on NMDAR dysfunction. Another reason for negative results could be inappropriate timing of recording or insufficient single-deviant paradigm.

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References
High frequency repetitive transcranial magnetic stimulation of the left DLPFC in treatment-resistant major depressive disorder: a randomized sham controlled trial - Preliminary results of the DREAM study
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Objective
To investigate the efficacy of high frequency repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) in the treatment of treatment-resistant major depressive disorder (MDD).

Methods: Twenty patients diagnosed with unipolar major depressive disorder without psychotic symptoms and qualified as treatment resistant were randomized to receive either 20 sessions of real or sham rTMS. Each session consisted of 60 five second trains at 10 Hz stimulation frequency and at 110% motor threshold, each train followed by 25 second pause. Treatment was administered five days per week for four weeks. Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HDRS), and score changes were compared between the two groups. Additionally, questionnaires regarding overall health status and symptoms were assessed.

Results
Neither group showed a significant improvement on the HDRS after treatment. The sham group showed more improvement than the treatment group but changes were not statistically significant. In line with the negative primary outcome measures, no significant changes on secondary measures including quality of life or global functioning were observed.

Limitations
These preliminary results are limited by the number of patients included thus far.

Conclusion
These preliminary results do not support the effectiveness of high frequency rTMS to the left DLPFC in treatment-resistant MDD patients that previously received all or most biological treatment options.

Trial registration
Current Controlled Trials ISRCTN73824458

Competing interests
None
Comparison between SMR and Upper Alpha Neurofeedback trainings as a non-pharmacological treatment of ADHD and sleep disorders in children and adolescents

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Background

About 5% of school-aged children may have an Attention Deficit-Hyperactivity Disorder (ADHD), a neurodevelopmental disorder often associated with other comorbid conditions including sleep disorders. ADHD became a public health concern. Psychostimulants are the first line pharmacological treatments for ADHD. However, parents are often reluctant to medicate their children and, additionally, a proportion of patients stop their treatment because of side effects. Non-pharmacological treatments are also available. Recently, improvements of cognitive functioning and hyperactivity level of patients with ADHD have been reported after Neurofeedback trainings with a relative Upper Alpha Power enhancement paradigm. Sensorimotor rhythm (SMR) Neurofeedback has been also proposed to improve ADHD symptoms. The aim of this study is to compare the benefits of Upper Alpha and SMR trainings on ADHD symptoms and concomitant improvement of sleep.

Methods

In this controlled and randomized study, 60 French medication-free children and adolescents with ADHD aged from 8 to 15 years old will participate in 30 neurofeedback sessions. They will be assigned to either in either the SMR or the Upper Alpha training group. EEG, ADHD rating scales, cognitive assessment, and actigraphic records will be performed at pre-, mid- and post-training times, and 6 months after the end of protocol.

Results

The main expected outcome is the clinical reduction of at least 30% of ADHD symptoms, and we anticipated the superiority of Upper Alpha training over SMR in reducing hyperactivity levels. Improvement of sleep quality is a secondary outcome.

Conclusion

To date, no comparison between SMR and Upper Alpha Neurofeedback trainings with a significant number of sessions and enough patients in each group has been conducted. We hope to gain valuable insights into specific effects of both trainings on ADHD symptoms and sleep without any medication. This study would foster the development of research on Neurofeedback and its clinical applications, which are under-investigated in France.

Trial Registration

N°ID RCB 2016-A00655-46

Keywords

ADHD, Neurofeedback, SMR-Upper Alpha Training, EEG, non pharmacological treatment, sleep disorders
Effect of Tai-Chi and Cyclic Meditation on Hemodynamic Responses of the Prefrontal Cortex
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Background
Mind body based meditation techniques called Tai-Chi Chuan (TCC, a moving meditation) [1] and Cyclic Meditation (CM, a stimulation and relaxation meditation) [2] has been proven to reshape the patterns of brain structures and functional connectivity. TCC practices showed improvement in the brain functions associated with cognition, behavior and health [3]. Similarly, CM also reported improvement in midbrain region [4] associated with better information processing speed or improved motor speed [5].

Method and Materials
We evaluated the effect of Tai-Chi Chuan (TCC, a Chinese movement based meditation technique) and Cyclic Meditation (CM, an Indian traditional based stimulation and relaxation meditation technique) on the hemodynamic responses of the prefrontal cortex (PFC) activity and autonomic functions (such as R-R interval (RR-I of heart rate variability and respiration). These two meditation practices were compared with simple walking. Employing 64 channel near infrared spectroscopy (NIRS), we measured hemoglobin concentration change (i.e., Oxyhemoglobin [DHbO], Deoxyhemoglobin [DHbR] and Total hemoglobin change [DTHC]) in the bilateral PFC before and after TCC, CM and Walking in young college students (n=25; average mean age ± SD; 23.4 ± 3.1 years).

Results
We observed the left PFC activity predominantly modulates sympathetic activity effects during the Tai-Chi whereas CM showed changes on right PFC with vagal dominance. However, the changes in oxyhemoglobin and total blood volume change after Tai-Chi was significant higher (p<0.05, spm t-maps) on left hemisphere, whereas after CM, there were a significant increase in oxyhemoglobin (p<0.01) with a decrease in deoxyhemoglobin (p<0.05) on right PFC. The normal walking showed decrease in Oxyhemoglobin with increase in deoxyhemoglobin on left PFC. The autonomic functions result showed a significant increase in RR-interval (p<0.05) along with significant reduction in HR (p<0.05) in CM whereas Tai-chi session showed significant increase in HR (p<0.05) when compared to walking session. Within group analysis showed a significant reduction in RR-I and significant increase in HR both in Tai-chi and walking sessions. The CM showed there were a significant improvement in RR-interval of HRV (p<0.01) with reduction of heart rate and breath rate (p<0.05).
Conclusions
The result suggested that Tai-Chi and CM both have positive effect on left and right prefrontal cortex and increase sympathovagal balance (alertful rest) in autonomic nervous system activity.

Keywords
Tai-Chi-Chuan (TCC); Yoga; Cyclic Meditation (CM); Walking; Prefrontal Cortex (PFC); Heart Rate Variability (HRV)

References
Assessing the dynamical instabilities of spontaneous EEG spectral and phase activity over time for capturing drug effects in Humans

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Background

EEG Oscillations of the drug behavior of various mental states around instabilities are interpreted using the concept of pragmatic information index[1]. It is demonstrated that this concept contains aspects of two different approaches in terms of the description of the brain as a self-organizing system. We integrate two approaches i.e. efficiency and entropy production into single measure of pragmatic information. Then we can understand how complexity and dynamics can be analyzed in one measure.

Pragmatic Information Index-PIE[2] is denoted by the logarithmic ratio of analytic Amplitude squared pattern (AM) intensity to the rate of pattern change estimated from the differences in normalized patterns (Freeman, 2004a). After preprocessing (filtering and ICA correction) steps, Hilbert transform is applied on each 3 seconds trial to get analytic amplitude (AM), denoted as $A_j(t)$, as a complex value for $j=1 \ldots 14$ channel numbers. The mean square, $A^2_j(t)$ is calculated for the EEG time series on each channel over an estimated time window ($\hat{W} = t_1 - t_2$).

$$A^2_j(t) = \sum_{t_1}^{t_2} [A_j(t)]^2$$

At each digitizing step this moving window is centered. The 16 mean squared amplitudes are formed a 14x1 feature vector as a point in 14-dimensional space. The arithmetic mean of the 14 values, $A^2(t)$, explains the normalized energy of the AM (Amplitude modulation patterns of various brain regions) in beta (8-40 Hz)-gamma (20-80 Hz) bands.

$$\log_{10} H(t) = \frac{A^2(t)}{D_\phi(t)}$$

where $D_\phi(t)$ is calculated by the Euclidian Distance between successive pairs of points in 16-electrode spatial space at $t$ and $t-1$ i.e. $D_\phi(t) = \| A^2(t) - A^2(t-1) \|_t$ is a digitizing step i.e. one step is 4 msec for 250 Hz sampling frequency! Consequently we have $H$ frames in beta and gamma ranges.

EEG data were recorded from 10-20 channel EEG with low pass and ICA corrected. The measured EEG activity is under vigilance-controlled and resting with closed eyes conditions. Our hypothesis is based on an assumption that time locations of stable AM patterns of high intensity using Hilbert transform will denote effects of pharmacological drugs on the central nervous system. The patient is in either stable or unstable course can be easily tracked using this new approach. We will be able to understand pharmacosensitivity [3] of the drug upon the duration of window length, threshold and minimal durations.
Results
We found highly linear statistical significance for each electrode between PIE values and the probabilities of those values with different slopes between control and bipolar disorder frames and evaluated.

Conclusions
Future research will be based on machine learning techniques for classification of various drug effects analyzed from frames.

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Efficacy testing of plant-derived and homeopathic drugs still remains a challenge in pharmacology. In the past several neurophysiological techniques have been successfully applied. However, interpretation of spectral power values with respect to different brain regions is contradictory. Conventional quantitative EEG analysis uses averaged data from epochs of 2 or 4 seconds. Analysis of shorter epoch length of 364 ms has been achieved by definition of specific frequency ranges [1]. Surprisingly, focal spectral power within these short periods reached tremendous values (up to 9000%) at single brain regions when compared to the average of other assessed regions (global median) [2]. In order to learn more about these short periods of high electric activity, EEG analysis was combined with eye tracking. The eye tracking software served to present different cognitive and emotional audio-visual challenges in series. Synchronization of the gaze overlay video from the eye tracking with screen capture of the online quantitative EEG analysis was achieved by starting the recording with a gong. The combined technology has been published [3]. Synchronized scenes were evaluated before and after intake of the preparations. In the presence of cognition activating drugs (i.e. Zembrin®) more flashing of delta (1.375 - 4.125 Hz) and theta spectral power (4.125 - 6.875 Hz) was observed in frontal brain in comparison to placebo during performance of psychometric testing. In the presence of calming drugs (i.e. plant-derived drug Pascoflair®) more flashing of alpha1 spectral power (6.875 - 9.625 Hz) was recognized in comparison to placebo. The same increase of spectral alpha1 power was detected after intake of 6 homeopathic Calmvalera Hevert tablets at a time. Since about 3 pictures per second are difficult to follow, slow motion videos will be presented. Finally, averaged data were fed into a discriminant analysis. Comparison of several plant-derived and homeopathic drugs with each other revealed for example projection of data from 3 calming drugs in close vicinity to each other.

References
The lateral phenotype and EEG patterns as predictors of the clinical prognosis of Tourette's syndrome
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In the past 20 years, investigators have turned increasingly to in vivo neuroimaging approaches to localize, quantify, and characterize anatomical and functional distinctions in subjects with Tourette syndrome (TS) [1]. It is suggested that TS is heterogeneous from a variety of standpoints including clinical presentation, psychopathology, and thus neuropharmacological responses.

Little is known about the long-term prognosis of TS [2].

We perform a retrospective analysis of the clinical presentation, efficiency of treatment and EEG characteristics (expression of the rhythms, gradient, asymmetry). It was examined 146 suffering from the TS patients. The average age of the subjects to the beginning of follow-up 8 years, the average duration of observation was 6 years.

Information about the lateral phenotype, dominant frequency EEG rhythms and their topography power was analyzed, as well as the dynamics of the clinical state.

As a result of the study, all patients were divided into 2 groups. The first group was characterized by the development of hyperkinesis downward, marked lateral right-brain dominance profile. Occipital-frontal gradient was saved. EEG was characterized by an increase in the power of alpha and beta rhythms. This group is characterized by a more favorable course with remissions in summer.

The second group consisted of patients who had corporal tics and stereotypies elements. The clinical picture is dominated by vocalization. Common EEG pattern for this group was characterized by increasing of alpha activity power in the left frontal lobe.

Thus, right hemisphere dominance and presence of physiological EEG gradient are favorable prognostic factors for this syndrome.

Keywords
EEG, Tourette syndrome, lateral phenotype, predictors

References
Comparative analysis of brain bioelectrical activity localization depending on neurophysiological age
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Human brain maturation is a complex, lifelong process that examined now in many studies. We focus on localizations of EEG activity changes observed in healthy adults, children, and contrast them with abnormal developmental changes in attention-deficit-hyperactivity disorder (ADHD).

This research with the hypothesis that the formation of deviance behavior as a consequence of immaturity frontotalamical regulatory system of the brain.

We search sources of EEG activity in the alpha band depending on the degree of maturity of the regulatory departments of the central nervous system.

10 minutes resting EEG-recordings with closed eyes was assessed in 5 unmedicated healthy persons from 17 to 23 years old, 5 children from 9 to 10 years old with ADHD and 5 healthy children with same age and without behavior problems.

The localization of the alpha-activity sources and statistical analysis of differences in the groups were carried out using the sLORETA software package [2].

As a result, a greater activity in prefrontal brain regions (Brodmann 11 field) was detected in healthy children compared with ADHD children. A similar comparison of students and children without behavioral disorders showed greater activity in medial parietal and occipital areas (Brodmann fields 31, 19) in a group of adults. Group of healthy children and students not differed significantly.

Thus, by comparing the EEG differences were found significantly different localization of alpha activity in a ADHD group. These differences may be used in the identification and objective evaluation of the formation of personality and behavioral characteristics delay.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest
The authors declare that they have no conflict of interest.

Keywords
EEG, ADHD, adults, children, sLORETA

References
Quantitative EEG assessment of students with ADHD undergoing neurofeedback training
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Several studies have demonstrated abnormalities in quantitative electroencephalogram (qEEG) in children and adults with ADHD. Based on these findings, neurofeedback training (NFT) has emerged as a new treatment option for ADHD. In this preliminary study, qEEG was used to assess the efficacy of NFT training for college students with ADHD. Participants received computer attention training intervention using NFT two times a week over a period of four months. A group of college students with ADHD who did not undergo NFT training was used as a control group. Brain activity was measured using qEEG prior to, midway through, and post NFT training. ADHD behavioral symptoms were also assessed pre- and post- training using the Conners’ Adult ADHD Rating Scale (CAARS-S:L) and the IVA-2. Changes in qEEG were detected following NFT. Significant changes in resting-state brain activity were observed in the experimental group. Participants who underwent training demonstrated significant decreases in absolute power across a wide spectrum of frequency bands (delta, theta, alpha and beta) as well as a relative decrease in alpha activity and increase in delta and beta activity. In order to identify if anomalous patterns of brain activity were related to symptoms of ADHD, neuroelectric measures were compared to behavioral measures. Changes in neural activity in the experimental group correlate with improvements in ADHD symptoms. Although further research is warranted to determine the exact impact of NFT on the neural correlates of ADHD, these preliminary findings suggest that it might be a promising cognitive training treatment for students with ADHD.

Keywords
qEEG, neurofeedback, ADHD, ADD
Improving drug discovery using brain oscillations as biomarkers for movement disorders

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Movement disorders represent a group of neurological syndromes characterised by an alteration of voluntary and/or automatic movements. Here, we focused on Parkinson’s disease (PD) and essential tremor (ET), which are the most common forms of movement disorders.

Motor symptoms of Parkinson’s disease result from a dysfunction of cortico-basal ganglia circuits mainly due to dopaminergic neurons death in the substantia nigra pars compacta. A hypersynchronization of beta frequency oscillatory activity in these circuits has been described in both patients and animal models of the disease.

Essential tremor (ET) is characterized by the symptom of action tremor (which intensifies when the affected muscles are used). ET typically involves a tremor of the arms, hands or fingers. The classically-used animal model of ET is generated by the administration of the beta-carbolin harmaline in mice. Harmaline induces action tremors lasting several hours and the classical read-out is the recording of behavioural tremor frequency that occurs between 8 to 10Hz.

The aim of this poster was to provide two examples of the use of brain oscillations in preclinical drug development for movement disorders. Here, 1) we assessed the use of aberrant cortical oscillations in the unilateral 6-OHDA injected rat as translational biomarkers for drug development in PD, and 2) studied the effect of harmaline-induced tremor on cortical and cerebellar oscillatory activities. The sensitivity of these functional biomarkers was challenged with the reference drugs for each pathology.

In the 6-OHDA rat model of PD, we found a prominent beta band (~30Hz) in the motor cortex, which was inexistent in control Sprague-Dawley rats. Acute injection of the dopaminergic receptor agonist L-DOPA (6 and 20mg/kg) induced body rotations along with a significant reduction of the beta band. This treatment also induced a prominent 80-100Hz gamma increase. By contrast, the D2/D3/D4 agonist ropinirole at 0.2, 0.4, and 0.8mg/kg also decreased the beta band but caused only a slight gamma band increase.

We found that administration of harmaline (10-20-30mg/kg) in male C57BL/6J mice dose-dependently increased the cortical and cerebellar power in a wide 15-60Hz frequency range, along with action tremors. Pre-treatment with 20mg/kg propranolol, one of the first-line medications used in ET patients attenuated the tremors and decreased the 35-60Hz range.

In this study, we identified aberrant EEG oscillations in two rodent models of movement disorders. These oscillations and their pharmacological modulation may represent predictive biomarkers for the identification, selection and validation of new therapeutics in movement disorders.
Telemetric electroencephalography (EEG) and in vivo microdialysis to study dopaminergic hyperactivity in freely moving rats
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Dopamine is a key regulator of cognition, mood, reward and movement in the human and rodent brain. The dopamine homeostasis is tightly controlled by the dopamine transporter (DAT), which is a target for addictive drugs (such as cocaine and amphetamine), and therapeutic antidepressants.

The present study was designed to investigate the effects of cocaine in freely moving rats using telemetric electroencephalography (EEG) to monitor a hyperdopaminergic state. Additionally, in vivo microdialysis in the nucleus accumbens shell was carried out to measure extracellular cocaine levels and dopamine itself by LC-MS-MS and HPLC coupled to electrochemical detection. Behaviour was assessed by an automated motor activity system using light beam interruptions.

Cocaine (5, 10 and 15 mg/kg, i.p.) dose dependently induced an increase in motor activity, which reached its maximum level after 20 min and lasted for 90 min. In addition, cocaine appeared to affect the EEG power spectrum, increasing gamma frequency band power up to 60 min after administration, whilst causing a decrease of power in delta, theta, alpha, and beta frequencies. Maximum cocaine levels measured from the dialysates appeared 30 min after dosing (300 nmol/l) and extracellular dopamine levels showed a peak concentration at 30 min and then returned to basal levels 120 min later.

In conclusion, these results indicate that cocaine induces an increase in dopaminergic transmission in the nucleus accumbens shell, and as expected, produces hyperactivity. The effect observed on the EEG frequency bands and in vivo microdialysis could serve as a physiological biomarker of target engagement studies and to set up a PK-PD relationship in drug discovery research.
Effects of clozapine on auditory steady-state response in schizophrenia
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Auditory steady-state responses (ASSR) provide a non-invasive technique to assess neural synchrony at a particular frequency. Attenuated phase-locking (PLI) of ASSRs in gamma frequency range is observed in schizophrenia and in animal models for psychosis [1]. State-sensitivity of 40 Hz ASSRs has been shown for schizophrenia, where PLIs increased with eyes closure in patients [2]. The effect of clozapine, which is prescribed in cases of treatment-resistant schizophrenia, on ASSR in humans is not clear. The aim of this study was to evaluate the effect of clozapine use on phase-locking of 40 Hz ASSR and state-sensitivity in schizophrenia patients.

48 male patients with schizophrenia (according to ICD-10 criteria) were recruited from the in-patients of Republican Vilnius Psychiatric Hospital. Patients were divided into two groups: (1) resistant to standard antipsychotic medication and treated with clozapine (Cloz, n=23); and (2) responsive to standard antipsychotic treatment (NCloz, n=25). ASSRs to click stimuli at 40 Hz were recorded using 9 channels in eyes open and eyes closed conditions, with 60 stimuli presented binaurally per condition. After conventional cleaning procedures, epochs of 700 ms were created starting at 100 ms prior to the stimulus onset and lasting for 600 ms post-stimulus. ASSRs were analyzed from Cz location, showing maximal activity. Mean phase-locking index (PLI) within 38-42 Hz window was calculated for 100 ms bins and subjected to RM-ANOVA with time bin and task as within-subjects factors and group as a between-subjects factor.

Significant interaction of condition (eyes open vs eyes closed) and group (Cloz vs NCloz) factors (p=0.038) was observed. This suggests that in Cloz group subjects tended to have lower PLIs in open eyes (p=0.08), which increased with eyes closure (p<0.001). In NCloz group, PLIs did not change with eyes closure (p>0.05).

Our data propose that state-sensitivity of 40 Hz ASSRs vary depending on the treatment in patients with schizophrenia, subject receiving clozapine showing response increase with eyes closure in contrast to those on standard antipsychotic treatment.

Competing interests
The author declare that they have no competing interests

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References
Neuro-Cardiac-Guided TMS (NCG TMS)**: A new and cost-effective method for accurately localizing the DLPFC in the treatment of depression.

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Background

The efficacy of rTMS in the treatment of major depressive disorder (MDD) has been well established in recent years. Most studies to date have employed the ‘5-cm’ rule for targeting stimulation of the Dorsolateral Prefrontal Cortex (DLPFC). New variations and improvements of this targeting technique include a ‘6-cm’ rule, the Beam-F3 method, and neuronavigated rTMS. Furthermore, it has been proposed that the efficacy of rTMS in MDD is more related to stimulating the area that is functionally connected to the subgenual anterior cingulate cortex (sgACC) rather than to specific cortical areas (Fox et al., 2012). Therefore, we set-out to develop and test a new method that employs knowledge about the functional role of the sgACC to establish in real time if the right cortical area is targeted. Method: Several studies have shown that areas in the ventromedial prefrontal cortex are involved in parasympathetic regulation such as heart rate and respiration, and that neurostimulation of these areas led to heart rate decreases (Makovac et al., 2016), most likely through connectivity with the nervus vagus. Therefore, based on the notion that rTMS aims to transsynaptically stimulate the sgACC, we used electrocardiogram (ECG) R-peak triggered single pulse TMS to various frontal locations to establish the location that most consistently resulted in a lengthening of the R-R latency (reflective of a heart rate deceleration). This method of Neuro-Cardiac-Guided TMS or NCG TMS thus could be the equivalent of what the Motor Threshold is for the motor system, but then for the DLPFC with heart rate as an output. Results: First preliminary results using a burst of 10 Hz TMS stimulation demonstrated that in a subject with a relatively large head circumference, no response was found at the ‘5 cm’ site (corresponding to FC4 in this subject), whereas the F4 location did result in a consistent heart rate deceleration. More data are currently being collected using a single pulse R-peak triggered approach and data will be presented.

Conclusions

In the treatment of MDD, Neuro-Cardiac-Guided TMS has the potential to become the equivalent of the ‘motor threshold’ for the DLPFC, and thereby would be a cost-effective and easy to use method for localizing the right stimulation target in the treatment of MDD, and also serve as a real-time control of adequate coil contact in patients undergoing rTMS treatment.

Electroencephalogram connectivity in frontal networks to predict outcome of electroconvulsive therapy in major depressive disorder
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Background
Major depressive disorder (MDD) is a common and potentially lethal disorder affecting up to 14% of all persons worldwide. However, 1/3 to 2/3 of patients are non-responders to first line therapy [1]. Even the electroconvulsive therapy (ECT) as the option of choice in therapy-resistant MDD still shows a high proportion of non-responders [2]. Due to the invasive nature of the ECT it would be desirable to know which subjects are likely to respond. In case of a predicted non-response to ECT, e.g. by means of electrophysiological electroencephalogram (EEG) parameters, other therapies of MDD (e.g. augmentation, polypharmacy etc.) could be chosen.

Methods
In this study, we retrospectively analysed two minute resting state EEG from patients with MDD who underwent ECT (4 - 12 sessions with 3/week) between 2005 - 2015 at the University Hospital of Zurich. Following several lines of evidence, we hypothesized altered non-linear connectivity in frontal networks including subgenual-, dorsolateral- and medio- prefrontal cortices being predictive for treatment outcome. Symptom severity and response/remission rates were assessed using the Global Clinical Impression (GCI) rating scale. Source estimates and connectivity measures were mapped using Low Resolution Brain Tomography (LORETA).

Results
Responders in comparison to non-responders showed a significant stronger non-linear connectivity in the frontal network within the EEG delta, alpha 1 and beta 1 frequency bands, while connectivity was weaker in theta, alpha 2, beta 2 and gamma frequency bands. Additionally, there were several non-significant correlations (from r = .15-.20) between symptom change and source estimates with e.g. a low midline theta-activity being associated with response to ECT.

Conclusions
Pre-treatment EEG-connectivity in frontal networks seems to have a predictive value for the efficacy of ECT treatment. Prospective trials and larger study groups are needed to further validate these markers and pave the way for possible usage in the clinical context.

Trial registration
Project ID: 2016-00562, Swissethics

No competing interests

References
Modulation of the serotonin system in an animal model of psilocin-induced psychosis: a network clustering approach
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Introduction
The present contribution deals with a particular study on animal model of psilocin-induced psychosis. QEEG methods addressing brain activity under certain set of conditions are usually based on bottom-up strategy preserving the low-level information e.g. coherence between two electrodes within particular frequency band at certain time after administration of a specific drug. Unfortunately, this approach leads to a combinatorial explosion if the effects of more drugs and their combinations are to be analyzed. This phenomenon makes data difficult to interpret. Here, we propose a way towards top-down strategy based on capturing an interpretable substance fingerprints. We show that unique functional brain clusters coherently modulated by a particular substance are embedded in multi-dimensional space of coherences and can be extracted by appropriate dimensional reduction technique [1].

Methods
The proposed technique takes coherences from 36 electrode pairs calculated in six discrete frequency bands (1-40Hz) at four specific time intervals (base line record, 20-30, 50-60, and 80-90 minutes post administration) and returns coherent topographic clusters. Our approach can be described in five following steps:
Coherence partial differences are calculated to extract functional changes between time intervals.
Coherence differences are processed by t-Distributed Stochastic Neighbor embedding (t-SNE) [2] to reduce data dimensionality on one hand and encode the original data structure on the other hand.
The silhouette clustering criterion is employed to determine a number of clusters in data [3]
The k-means algorithm categorizes data into clusters determined in step 2 and 3
Obtained electrode pair clusters are visualized in topographic view.

Results
Psilocin clearly shows four functional clusters which are precisely symmetric in topographic view and which exhibit a global maximum of clustering criterion. In similar way, 5HT2A antagonist MDL-100907, and clozapine result in three clusters. This is in contrast with saline solution exhibiting no clustering and no global extremes of clustering criterion. Generally, all antagonists in combination with psilocin lead to less or no clusters.
Conclusions

The proposed technique is capable to contrast long term dynamics of coherences and find functional brain structures coherently modulated by a particular drug. This allows us to further study the mechanism behind the psilocin induced functional disconnection — the functional changes are specifically organized. All antagonists seem to compensate the psilocin induced organization. Our next step is to apply the technique in human psilocybin model of psychosis and search a new translation bridge between animal and human models.

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I declare no conflict of interests.

References


Clonidine Augmentation Therapy in Schizophrenia “CATS-Study”
A promising new treatment strategy in resistant schizophrenia
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Background
Deviations in basic information processing, such as sensory gating, are thought to underlie cognitive deficits in schizophrenia. Treatment with the current first- and second-generation antipsychotics show almost no improvement in these early information processes. In parallel, there is little or no success in treating cognitive deficits with these drugs. In a recently conducted pilot-study from our laboratory we found that administering a single dose of clonidine, a noradrenergic α2A-receptor agonist, restored sensory gating in patients with schizophrenia to a level that no longer differed from an age and gender matched control group. It is expected that improvement of early information processing leads to improvement in cognition.

Goal
Improving currently available antipsychotic medication by normalizing early information processing.

Methods
Randomized Clinical Trial (RCT), conform to a randomized, balanced placebo-controlled design with two arms: in condition 1, patients (n=25) will receive 6 weeks of additional clonidine treatment to their current medication, in condition 2, patients (n=25) will receive 6 weeks of additional placebo treatment to their current medication. In addition, 25 age and gender matched healthy subjects will function as controls. Primary outcome is change in symptom severity, expressed as a change in total score on the Positive and Negative Symptom Scale (PANSS) from baseline to end of the 6-week treatment. Secondary outcomes are changes in cognitive functioning (measured through the Brief Assessment of Cognition in Schizophrenia; BACS and Cambridge Neuropsychological Test Automated Battery; CANTAB), change in GAF (global assessment of functioning) scores and the measurement of various psychophysiological parameters of basic information processing, such as P50 suppression, prepulse inhibition of the startle reflex (PPI) and mismatch negativity (MMN).

Results
In line with our pilot-study it is expected that early information processing will improve. We predict that this will lead to an improvement in cognitive functioning after six weeks, which expectantly leads to lower symptom severity and a better quality of life.

Trial Registration
EudraCT Number: 2014-003008-53
Isolated epileptiform discharges: an electroencephalographic abnormality underlying medication failure in autism spectrum disorder

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Background
Autism Spectrum Disorder (ASD) often presents a treatment challenge due to the variety of symptoms that make each case unique. Medication prescribed to manage ASD associated symptoms such as anxiety, depression, attention issues, and behavioral problems often fail to alleviate symptoms and can produce undesirable side effects. The question is, why are the stimulants, selective serotonin reuptake inhibitors, and antipsychotics prescribed to alleviate these issues [1] effective in some patients but fail in others? The answer could be related to the increased prevalence of electroencephalographic abnormalities in psychiatric patients [2]. The presence of isolated epileptiform discharges (IEDs) may account for the treatment failure of these medications, especially antipsychotics, because these drugs lower seizure threshold, thus resulting in increased epileptiform activity. Electroencephalography (EEG) can be used to document the presence of IEDs that would otherwise go undetected. The purpose of the study was to reveal the prevalence of IEDs in the ASD patient population and to demonstrate the usefulness of the EEG for providing data to psychiatrists, neurologists, and developmental pediatricians to improve medication selection and outcomes for patients with ASD.

Method
The data was obtained from an Institution Review Board approved data archive from a multidisciplinary practice that treats a wide variety of refractory and neuroatypical patients. The study is comprised of 140 non-epileptic children, adolescents, and adults diagnosed with ASD, ages 4 to 25. A board certified electroencephalographer interpreted the EEGs in order to identify abnormalities.

Results
Of the 140 patients with ASD, 36.4 percent were found to have IEDs after a EEG screening. Chi-square analysis found no significant difference between genders among the three age groups. The findings indicate a high prevalence of IEDs among individuals with ASD.
Conclusion
Our results find that compared to the healthy population, a large number of patients with ASD have IEDs despite never having a seizure. The findings support the use of EEG in children, adolescents, and young adults with ASD, regardless of gender or age. This is particularly true for those who have failed prior medication attempts with stimulants, antidepressants, and/or antipsychotics. Utilizing the EEG for refractory cases in a psychiatric practice allows for more individualized and precise medication selection.

Consent to publish
This study does not contain details relating to individual participants.

Competing interests
The authors declare that they have no competing interests.

References
Neuromodulation using maintenance TDCS optimized by qEEG leads to full recovery from myalgic encephalopathy/chronic fatigue syndrome: A case report
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Background
A 61-year-old man with progressive myalgic encephalopathy (ME/CFS)** was referred for neuromodulation. His condition, likely virally induced decades ago, was characterized by recurring periods of extreme fatigue, lasting months at a time. Severe fatigue had become unrelenting over the prior two years, impairing many dimensions of his life. Multiple immunological and neurological work-ups were negative and fibromyalgia had been ruled out. Patient failed many medically advised approaches, including antidepressants, acupuncture and a gluten-free diet.

Methods
Genetic analysis suggested he would respond to dopaminergic agents and to neuromodulation [1]. Trials of both amphetamines and methylphenidate ultimately failed but modafinil 200 mg did provide partial relief. Distance from the office precluded daily treatment with repetitive transcranial magnetic stimulation (rTMS). Transcranial direct current stimulation (tDCS) was chosen as a safe alternative feasible treatment [2], allowing cumulative, ongoing treatment to target ongoing inflammation. We used neurophysiological state markers of qEEG. Patient was trained with tDCS in the office and then treatment was self-applied at home daily with anode on left dorsal-lateral prefrontal cortex (LDLPFC), cathode on right (RDLPFC), 2 mA/min, 20 minutes, 40 mA total dose, using 1.5” diameter electrode pads. After four weeks, maintenance tDCS sessions were increased to twice daily (6 AM and 12 Noon) and modafinil was lowered to 100 mg.

Results
Follow-up qEEG testing was done one year after the initial qEEG when patient was in full recovery. Comparison of pre-treatment and post-treatment qEEG findings show minor improvement in excessive hypercoherent frontal alpha, a substantial 50% drop in excess left temporal alpha, and a normalization at the very low end of the qEEG spectrum (less than 1 Hz). The patient noted: “[this treatment] has given me sustained relief from a chronic fatigue condition from which I’ve suffered throughout my adult life.”

Conclusions
Maintenance treatment with daily tDCS and modafinil likely exerted synergistic effects on the brain and immune system. The clinical recovery with notable improved sleep, energy, and ability to tolerate exercise are most likely to be reflected in slow wave
oscillation changes. This case supports the need to look more closely at glial as well as neuronal impact, perhaps expanding qEEG to include slow wave markers. Clinicians are eager to have qEEG personalized biomarkers to optimize adjunctive tDCS stimulation in chronic psychiatric and neurological conditions, so often neuroinflammatory in nature [3].

** The Myalgic Encephalopathy Association feels that myalgic encephalopathy is a more appropriate term than the original myalgic encephalomyelitis. The condition is more commonly known as chronic fatigue syndrome.

**Keywords**
tDCS, myalgic encephalopathy, chronic fatigue syndrome, neuroinflammation, qEEG biomarker, personalized medicine

**Consent to publish**
Informed consent was obtained and the subject's rights were protected.

**Competing interests**
No competing interests

**References**
Changes of CNS- and ANS arousal levels following successful antidepressant treatment with ketamine: A case series
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Introduction
Ketamine has been established as an alternative in the treatment of therapy-resistant major depressive disorder (MDD). Although response rates are reportedly high with up to 60-70%, until now no biomarkers that could predict treatment response exist. As a first step, this case series aimed at identifying electrophysiological markers of arousal that reflect alterations of ongoing neuronal activity after treatment with ketamine.

Methods
Two patients (one 65-year-old female, one 78-year-old male) with therapy-resistant depression (> two treatment -approaches with SSRIs, SNRIs or TCAs) were treated with ketamine infusion four times respectively six times during three weeks. Resting state electroencephalogram (EEG) and electrocardiogram (ECG) were recorded at baseline and after treatment with four /six time ketamine infusion. Central nervous system (CNS) arousal was assessed using Vigilance Algorithm Leipzig (VIGALL). Autonomous nervous system (ANS) function was quantified using heart rate and heart rate variability measures (HRV). Changes of depressive symptoms were assessed using Hamilton Depression Rating Scale (HDRS).

Results
Both patients showed a marked decrease of depressive symptoms with a drop from 28 HDRS to 9 HDRS after four ketamine infusions and from 20 HDRS to 6 HDRS after six infusions respectively. In parallel, both patients showed a decrease of CNS arousal levels as assessed by VIGALL with increased amounts of low vigilance stages and decreased EEG-alpha peak frequencies after therapy in comparison to baseline EEG recording. Further, both patients revealed a lowered ANS arousal level as assessed by a reduction of heart rate >24h after the last ketamine infusion in comparison to pretreatment condition.

Discussion
Following the arousal framework in MDD with a suggested high EEG-vigilance level in depression, the found decrease of CNS-arousal could be interpreted as a consequence of the anesthetic, i.e. vigilance decreasing effect of ketamine. In contrast, the decrease of heart rate remains elusive in the light of an initial increase of sympathetic function following infusion of ketamine. However, decrease of CNS- and ANS arousal level could lead to less pronounced MDD related behavioral aspects such as withdrawal and sleep disturbances. The predictive value of the EEG in ketamine treatment should be in the focus of further prospective randomized studies.

Consent to publish
Written informed consent has been obtained by all patients prior to publication.

Competing interests
The authors report no competing interests
ECoG spectral analysis of the Interaction between caffeine and nicotine
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Caffeine and nicotine are the most consumed psychostimulants worldwide. Although the electrophysiological effects of each drug alone were studied extensively, the literature on the effects of their combined treatments on brain electrical activity is scarce. The present study aims to investigate the effects of the intraperitoneal injection of caffeine followed by the subcutaneous injection of nicotine after 1 h on electrical activity recorded from the cortex of rats (ECoG). It was found that the successive injection of caffeine and nicotine resulted in a significant increase in the power of delta frequency band but a significant decrease in the power of theta, beta-1 and beta-2. It was suggested that the caffeine and nicotine interaction could have an adverse effect by altering the cortical electrical activity that may indicate impair in memory encoding.
Dishabituation of central nervous system to tonic pain following chiropractic care - a standardized low resolution brain electromagnetic tomography (sLORETA) based study

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It has been demonstrated that after chiropractic spinal manipulation neural plastic changes occur in different areas of the brain. Different methods have been utilized to assess these changes, but the majority of the measurements to find the involved brain areas have been indirect. The objective of this study was to determine the changes in brain activity during tonic pain after single session of chiropractic care in a sub-clinical pain population by using source localization of the EEG.

Fifteen healthy volunteers (10 males, 32.1 ± 7.2 years) participated in two experimental sessions on separate days; chiropractic or control (sham) session in random order. The EEG was recorded continuously using a 61-channel system before and after either intervention during 72s of cold pressor test at 2°C (left hand). The pain and unpleasantness ratings were obtained on two separate numeric scales (range: 0 = no unpleasantness/pain to 10 = maximum unpleasantness/pain). The EEG was divided into 9 epochs (8s each), which were separated into four frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (12-32 Hz). Subsequently, standardized low resolution brain electromagnetic tomography (sLORETA) was done on these frequency bands.

In the control experiment, the brain activity decreased in all frequency bands (all p ≤ 0.05), whereas no change in activity was seen after the chiropractic session (all p > 0.05). The decrease in activity in the control arm was specifically seen in the limbic (delta), frontal (theta) and temporal (alpha and beta) lobes. The pain scores decreased in control arm (p < 0.05) whereas the unpleasantness scores decreased for both interventions (all p < 0.05).

The decrease in brain activity in the control arm reflects central habituation which occurs due to repetitive painful stimulation. The lack of this phenomenon in the chiropractic arm could imply that the chiropractic care normalizes the central nervous system leading to central dishabituation.
Animal 3D brain-mapping
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Introduction
To this date there are no standardized mapping methods that display animal cortical EEG on the brain surface. Therefore, this study describes a 3D imaging method to be used for EEG mapping on the surface of the rat brain. The aim of our study was to develop a software module and a standard for statistical brain mapping. Animal EEG data recorded during behavioral activity and inactivity served as a subject for analysis and brain mapping.

Methods
In this study we measured electrical activity of the rat brain. For imaging purpose, we used 3D brain model from atlas [1] and adjusted it for our own module. We confirmed the validity of the 3D brain model by comparing the dimensions of normalized brain scans of 9 rats of the Wistar strain typically used in our laboratories. We have created a MATLAB module for brain mapping with the use of the rat brain model and a possibility to place any number of electrodes on the surface of the rat brain. The spline interpolation was used for imaging activity on surface of the brain [2] and statistical brain-mapping was used to compare the two example behavioral conditions.

Results
The module was effectively used to display EEG activity on the 3D surface and to display the statistical group differences in the sample of the animal data between behavioral activity and inactivity. The module can also compare data from individual measurement with a group mean.

Conclusions
This study describes computation of splines interpolation curves that are important for the brain mapping in rats. This approach will be used for effective comparisons of brain activity of rats under various conditions and with variable number and placement of cortical electrodes.

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I declare no conflict of interests.

References
Ketamine on working memory - what are the underlying EEG correlates

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Neurodegenerative disorders are associated with a decline in working memory (WM) and thought to be accompanied by dysfunctional connectivity and altered theta/gamma amplitude within the hippocampal-prefrontal circuit (HC-PFC)[1,2,3]. The hippocampus and prefrontal cortex both have dense populations of N-methyl-D-aspartate (NMDA) receptors. Ketamine, a NMDA receptor antagonist, is of interest as a mechanistic model of glutamatergic dysfunction mimicking cognitive impairments in animal and human studies [4,5,6].

In this study, we sought to identify an EEG fingerprint of working memory under normal and impaired conditions of functional connectivity and amplitude in the theta and gamma frequency bands[7]. Long-Evans rats received a baseline saline injection followed by an acute and repeated sub-anaesthetic doses of ketamine (10 mg/kg, s.c.) 30 min prior to performing a Delayed-non-match to position task, and amplitude as well as functional phase based connectivity changes were studied in the retrosplenial, frontal association, lateral parietal association and cingulate cortex, with the cingulate serving as the seed [8].

The task showed to be measuring working memory, yet ketamine didn’t influence performance neither acutely nor after repeated exposure. The EEG revealed no specific effect of ketamine on working memory either, but we did identify an EEG fingerprint of WM, which showed a dissociation between amplitude and network connectivity for the different brain regions and frequency bands. The main effects of WM were found in the higher theta band in the network, whereas no changes were occurring in the gamma bands. Ketamine didn’t show an effect in the low theta band possibly owing to compensatory mental effort [9,10].

Working memory in this study didn’t show to be impaired by acute or repeated ketamine, which also was reflected in the behavioural data, not necessarily ruling out ketamine as a good model for degenerative diseases, as ketamine effects were visible, but might bear evidence for the task having been learned too well and/or the exposure to ketamine not being sufficient to functionally disrupt the system.

The author(s) declare(s) that they have no competing interests
References


Effects of γ-aminobutyric acid-modulating drugs on resting state brain oscillations and executive function in healthy volunteers: a pilot study

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Background
Recent findings have suggested a relationship between abnormal γ-aminobutyric acid (GABA) function, disordered neuronal oscillations, and impaired executive function in schizophrenia. Additionally, there has been an increasing amount of interest in the therapeutic potential of these drugs in the treatment of this disorder. However, the neural oscillations that underlie the effects of GABA-modulating drugs on cognitive functioning require further work.

Objective
In an attempt to begin identifying which receptor subtypes may alter the neural oscillations underlying executive function via selective agonist actions, the study examined the effects of: a) a benzodiazepine drug with broad spectrum agonist actions at all GABA receptors containing the α1, α2, α3, and α5 subunits, and the γ subunit (in addition to the obligatory β subunit) and b) a drug with agonist actions at GABAB receptors. The objective of this pilot study was to examine the effects of single doses of these GABA enhancing drugs on resting state brain oscillations and executive function in healthy volunteers stratified by executive function performance.

Method
30 participants were assessed in a randomized, double-blind, placebo-controlled design. Three minutes of eyes closed resting state brain oscillations were measured from 8 electrode sites in response to an acute administration of lorazepam (Ativan®; 1.0 mg), a GABA_A receptor positive allosteric modulator, and baclofen (Lioresal®; 10 mg), a GABA_B receptor agonist. Executive function was assessed using the Groton Maze Learning Task (GMLT) of the CogState Schizophrenia Battery.

Results
Spectral analysis revealed overall reductions in alpha and theta oscillations with the lorazepam treatment. Follow-up analyses indicated that these reductions were in the better performing participants. Correlational analyses revealed that greater lorazepam-induced reductions in alpha and theta oscillations were associated with greater lorazepam-induced cognitive impairment. Reduced theta at placebo was also associated with worse performance. Additionally, smaller theta activity at placebo was associated with greater lorazepam-induced cognitive impairment.

Conclusion
The results suggest that GABA_A-modulated alpha and theta oscillations are involved in the neural underpinnings of executive processing.
EEG machine learning for enhanced monitoring of Alzheimer's disease and cholinergic modulation

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Scopolamine is a muscarinic acetylcholine receptor antagonist (mAChR) that induces cognitive impairments resembling those observed in Alzheimer’s disease (AD) and schizophrenia. It is used in drug development to demonstrate the reversal of the temporary scopolamine-induced cognitive deficits by a cognition enhancing compound. However, there is an urgent need for biomarkers that monitor therapeutic response; current biomarkers lack the desired accuracy, because of the large variability in healthy subjects and the often subtle disease-related changes. In EEG, pathophysiology is often expressed in multiple ways. Here we show that an integrative approach in which any biomarker that carries complementary information about a disease or therapeutic intervention can result in an accurate diagnostic index for better decision making in clinical trials.

Recently, we showed that EEG biomarker integration improves the prediction of conversion from mild cognitive impairment to Alzheimer’s disease (AD) compared with a single-biomarker based prediction [1]. The integrative biomarker index can be used for stratification of patients at recruitment in clinical studies and for documenting and quantifying effects of intervention. Here, we provide additional proof-of-concept that EEG-based prediction can be improved with the integrative biomarker approach in clinical trials where a drug is tested in a scopolamine challenge model in healthy subjects.

For this purpose, we have developed an integrative EEG-biomarker index (mAChR index) that is optimally sensitive to the CNS effects of scopolamine, to objectively determine whether reversal of scopolamine effects by a cholinergic compound is successful. The mAChR index yielded higher classification performance than any individual EEG biomarker with accuracy, sensitivity, specificity and precision ranging from 88–92%. This significantly outperforms the single-best EEG biomarker (relative delta power). Validation on an independent dataset indicated the robustness of the index. To support the validity of scopolamine as a model for AD pathophysiology, we show that the mAChR index discriminates healthy elderly from patients with AD.

We address this by using novel features of the Neurophysiological Biomarker Toolbox (http://www.nbtwiki.net/), which employ data-mining algorithms to combine the information from multiple biomarkers. Our results demonstrate that integrating information from multiple EEG biomarkers can enhance the accuracy of identifying disease or drug intervention, which should be of interest to a wide range of clinical trials.

References
Midfrontal theta dynamics reflect the ability to overcome motivational biases in decision making
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Our motivations influence our actions in predictable ways. The promise of a reward promotes behavioural activation, while the threat of a punishment context promotes inhibition. However, these motivational biases can at times be at odds with our goals. At such times, we need to be able to suppress them, which has been suggested to be implemented by the midfrontal cortex. We developed a novel paradigm and computational models of behavior to disentangle the impact of such motivational response biases, from the impact of learning from reward and punishment outcomes. Participants (N=34) completed this task while recording surface EEG. As expected, cue valence strongly biased action. Midfrontal theta-band oscillatory activity was increased in those trials, where the motivational response bias conflicted with the required response, particularly when subjects successfully suppressed the motivational bias. We will present further analyses to dissociate the role of midfrontal cortex in learning from reward and punishment outcomes. This work will allow us to characterize how motivations drive biases in both choice and learning, and how we may learn to suppress these when they are at odds with our instrumental goals. This work has relevant implications for a range of psychiatric disorders associated with a maladaptive reliance on impulsive, motivation-driven responding including addiction, impulse control and ADHD.
Neurophysiological substrates of memory processes: assessment of glutamatergic and cholinergic modulation of sharp wave ripples in rats

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Sharp wave ripples (SPW-Rs) represent the most synchronous population patterns observed in the mammalian brain and are considered a cognitive biomarker for episodic memory and planning. SPW-Rs occur during several off-line states of the brain including non-REM sleep; are modulated by many neurotransmitter systems; and affect both cortical and subcortical structures by their excitatory output. Selective disruption of SPW-Rs impairs memory formation and pathological SPW-Rs have been observed in rodent models for neurodegenerative diseases. Quantification of these synchronous population patterns associated with memory processes is instrumental for a better comprehension of neurodegenerative diseases as well as for assessing the efficacy of novel pharmacological treatments. The purpose of this study was twofold: first, to develop and validate a novel computer-automated touchscreen-based spatial search task assessing either working memory or memory consolidation in Long-Evans rats; second, to quantify SPW-Rs’ activity in this spatial search task during working memory or memory consolidation combined with pharmacological glutamatergic and cholinergic modulation. For the working memory component of the task, rats had to find a hidden location on the touchscreen with either a short (2 sec) or long (10 sec) delay between 10 consecutive trials with each delay having 4 different locations presented within one session. During these delays, hippocampal SPW-Rs from the CA1 stratum pyramidale cell layer were measured following each completed trial, using implanted 4-shank silicon electrodes. Here, SPW-Rs were measured when the rat was moving at speeds of less than 4 cm/s, by use of video monitoring to ensure events analyzed were associated with quiescent periods only. Results indicate that Scopolamine 0.1 mg/kg but not 0.05 mg/kg decreased performance for the long but not for the short delay. For the memory consolidation component of the task, rats received 1-day or 4-day acquisition session/s of a single hidden location with variable encoding strength using few (<10) or many (>40) trials per session. Memory consolidation of the location was measured 24 hr after acquisition by the use of a probe trial. SPW-Rs were measured when the rats were asleep both before and after the acquisition session. A differential effect on encoding versus consolidation was addressed using pharmacological manipulation of glutamatergic and cholinergic systems. This study reinforces the strength of combining neurophysiological and cognitive behavioral assessment to further understand memory processes and effects of pharmacological treatments thereon.
Glutamatergic deficit and negative symptoms: new evidence from the ketamine model of schizophrenia
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Targeting the N-methyl-D-aspartate-receptor (NMDAR) is a major approach for treating negative symptoms of schizophrenia. The ketamine model of schizophrenia has the advantage of comprehensively producing schizophrenia like symptoms such as positive, cognitive and negative symptoms in healthy volunteers. The amplitude of the Mismatch Negativity (MMN), a neurophysiological parameter related to infrequent stimuli, is known to be significantly reduced in schizophrenic patients but also in healthy controls receiving ketamine [1,2]. Accordingly, it was the aim of the present study to investigate whether changes of MMN during ketamine administration are related to the emergence of negative symptoms in healthy subjects.

Therefore, we examined the impact of ketamine on MMN amplitudes and its sources (sources localization approach: low resolution electromagnetic tomography (LORETA)) by means of 64-channel electroencephalography (EEG) recording during performance of an auditory MMN paradigm and assessed the psychopathological status using the Altered State of Consciousness (5D-ASC) Rating Scale and the Positive and Negative Syndrome Scale (PANSS). Twenty-four male, healthy volunteers were measured with pharmacological EEG using a single-blind, randomized, placebo-controlled crossover design.

We identified significant changes of the MMN response, to both duration and frequency deviants, under ketamine condition as well as a significant increase in all PANSS scores. Reductions of MMN amplitudes were significantly correlated with more pronounced negative symptoms, assessed by the PANSS.

Accordingly, the MMN might represent a biomarker for negative symptoms in schizophrenia related to an insufficient NMDAR system and could be used to identify schizophrenia patients with negative symptoms due to NMDAR dysfunction and thus to determine a maximal benefit of drugs modulating neurotransmission at the NMDAR.

Competing interests
The authors declare that they have no competing interests.

References
Modulation of the serotonin system in an animal model of psilocin-induced psychosis – time course of quantitative eeg changes

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Introduction
The serotonergic hallucinogen psilocybin and its active metabolite psilocin nowadays receive a lot of attention in the scientific community as a research tool for modeling psychosis. First experiments assessing brain activity after psilocybin administration in humans using PET and fMRI found contradictory results [1,2]. More recently, a study directly measuring neuronal activity using MEG confirmed massive inhibition of brain activity [3]. The aim of our animal study was to assess psilocin-induced changes in quantitative EEG (QEEG) in rats in order to explore the role of different serotonergic receptors in psilocin action.

Methods
The substances used were: psilocin (4 mg/kg s.c.), 5HT1A antagonist WAY 100635 maleate (1 mg/kg s.c.), 5HT2A antagonist MDL-100907 tartarate (0.5 mg/kg s.c.), 5HT2C antagonist SB-242084 (1 mg/kg s.c.), haloperidol 0.1 mg/kg s.c. and clozapine 5 mg/kg i.p. For EEG experiments, rats were stereotactically implanted with 12 active electrodes onto the surface of the cortex under isoflurane anesthesia. EEG was recorded in freely moving rats after one-week recovery from surgery. EEG power spectra (local synchronization) and coherence (long projections) were subsequently analyzed comparing the drugs’ effect in time (20-30, 50-60 and 80-90 minutes post administration) to the baseline record. To avoid moving artifacts and effects of behavior on EEG, only EEG traces corresponding to behavioral inactivity were included in the analysis.

Results
Psilocin generally decreased both EEG absolute spectral power and EEG coherences. The changes in spectral power induced by psilocin were normalized partially by all substances used, mainly in the lower frequency bands. However, only 5HT1A and 5HT2A antagonists partially normalized the psilocin-induced decrease of EEG coherences. The specific QEEG pattern of each substance and the temporal dynamics of QEEG changes will be presented.

Conclusions
Psilocin-induced changes in QEEG in rats are very similar to our recent human data with psilocybin and are in accordance with the concept of psychosis as a disconnection syndrome. All the specific SHT antagonists and both antipsychotic drugs specifically
affected the EEG spectral power induced by psilocin. Surprisingly, only 5HT1A and 5HT2A antagonists were able to partially reverse psilocin-induced disconnection. These results indicate that 5HT1A and 5HT2A receptors might be involved in the increase of entropic brain activity during psychedelic state as well as acute psychosis.

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References


Novel methods assessing electrophysiological alterations by 5-HT2C receptor agonist CP-809,101 in sleep EEG and power spectral activity

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The serotonergic 5-HT2C receptor is a key contributor to a variety of medical conditions including psychiatric and neurological diseases. The development of therapeutic approaches at this receptor, with both, agonists and antagonists continues to be in focus [1]. Using a novel wireless EEG device (Neural Activity Tracker-1) and a novel in-house developed statistical algorithm we investigated electrophysiological changes in sleep structure and EEG power spectral distribution caused by the highly selective 5-HT2C receptor agonist CP-809,101.

In two independent studies, male Fischer rats with chronically implanted supracortical EEG-electrodes were treated with 10 mg/kg of CP-809,101. In the 1st study, sleep structure changes in terms of total sleep time, percent of time spent in different vigilance states, the number of rapid eye movement (REM) episodes, and latency to first sleep and REM episode were analyzed. Treatment with CP-809,101 led to attenuation of time spent in mild, deep, and REM sleep. It increased time spent in wake state and latency to first sleep and first REM episode.

The 2nd study investigated power spectral distribution changes. A refined statistical method of baseline-adjusted power spectral changes revealed an attenuation of delta and theta band by CP-809,101 in comparison to vehicle recordings while maintaining the delta/theta ratio. Our results clearly demonstrate that acute treatment with CP-809,101 changes both sleep architecture and power spectral parameters in Fischer rats.

5-HT2C agonists have been suggested to exhibit antidepressant-like profile that fits to the sleep changes observed in our study. Further, 5-HT2C agonists have been reported to inhibit theta oscillation, desynchronizing the EEG and leading to shifts to lower frequencies [2,3]. Yet, despite the inhibition of theta oscillation and desynchronization of the EEG by CP-809,101, the ratio between delta/theta revealed no changes underlying the wake-promoting effects of CP-809,101.

Disclosures
All authors are employees of AbbVie. The design, study conduct, and financial support for this research was provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

References
P300 in pharmacological models of psychosis
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Background
P300 (P3) is an index of focal attention processes and memory updating. Impaired cognition is one of hallmark features of psychotic disorders. Both psilocybin (5-HT2A agonist) and cannabinoids induce acute transient psychotic symptoms and have previously been used as putative models for psychosis. In order to investigate the extent of cognitive disruption during psilocybin and cannabis intoxication, information processing was evaluated by means of both sensory event related potentials (P2, N2) and cognitive potential P3.

Methods
Data from two separate studies are presented.
1) In a placebo-controlled design, 20 healthy adults were administered a dose of psilocybin per os (0,26 mg/kg) and placebo during 2 separate sessions.
2) In an ecologically valid model of cannabis intoxication, 34 recreational users, 32 chronic users and 30 healthy age- and gender-matched cannabis non-users were recruited. ERPs were recorded in a sound-attenuated room with each participant lying down with their eyes closed in a comfortable setting with two sitters (male and female) being present for the whole time. An oddball paradigm with 120 frequent and 30 target tones presented binaurally in a pseudo-random order was used. Data were acquired with a standard 32-channel digital EEG amplifier BrainScope (unimedis, Prague) with 20 active scalp electrodes and oculogram according to the 10/20 system.

Results
Psilocybin: A repeated-measures ANOVA on latencies and amplitudes of P2, N2 and P3 revealed significant effect of psilocybin only on P3 amplitude. Further analysis showed correlations between P3 amplitude and selected variables from objective and subjective rating scales. Cannabis: While the groups did not differ in P3 latency or amplitude, ANOVA revealed a main effect of group for P2 component with recreational users displaying smaller amplitudes than healthy controls. Furthermore, N2 latency in recreational users was shorter when compared to healthy controls.

Conclusion
In line with previous findings, psilocybin induced abnormalities in higher-order cognition. Impaired processing is likely to be related to heightened activity of the serotonergic system at the peak of psilocybin intoxication. Although P2 findings in cannabis model indicate attention difficulties, non-significant P3 results need to be considered as well and are discussed in light of the ecological validity of the model.

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I declare no conflict of interests.
Frontal alpha asymmetry in depression: Fact or fiction? A meta-analysis
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In major depressive disorder (MDD) research, frontal alpha asymmetry (FAA) has frequently been reported as a potential discriminator between depressed and healthy individuals, although contradicting studies and non-significant results have been published [1,2]. Locating an MDD biomarker could benefit many people, as MDD is predicted by the WHO to become the second most debilitating disease by 2020. The aim of the current meta-analysis is to clarify the relationships between MDD and FAA further, through analyzing new research from the last decade and put it in perspective by comparing current and past findings (for example a meta-analysis [1]).

Cohen’s d will be calculated from the means and standard deviations for FAA measures (subtracting mean log transformed left midfrontal alpha from mean log transformed right midfrontal alpha [ln(F4)-ln(F3)]), or a similar measure. Possible covariates including age, gender, handedness, year of publication, country of residence, depression severity, medication, EEG recording length, keeping eyes either open, closed or both, EEG reference, and used alpha frequency will be explored. A study will be included if the article (1) reports on both depressed and healthy individuals, (2) provides an FAA measure involving F3 and F4, and (3) provides all data regarding above mentioned covariates (reported either directly or obtained through contact with corresponding authors).

Preliminary results of our currently ongoing meta-analysis will be presented. On the one hand, previous studies have reported relative more left-sided alpha in MDD (sometimes only for higher frequency alpha and not for every EEG montage). On the other hand, non-significant and even opposite results have been reported, showing no baseline FAA differences between depressed patients and controls, or finding relatively more right-sided frontal alpha. Our expectation is that there will be no difference in FAA between MDD and non-MDD groups, based on more recent studies reporting contradicting results, as well as today’s largest investigated sample regarding this topic, the iSPOT-D study [2], showing non-significant results. If non-significance is indeed demonstrated, the use of FAA as a diagnostic tool can be questioned. Nevertheless, its contribution to other applications (such as treatment prediction) could be further explored.

References
Neuropharmacological profile of selected areas responsible for the inhibition of P50 wave: from the P50 wave to off-label treatment of schizophrenia.

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Patients suffering from schizophrenia have been shown to exhibit impaired P50 ERP amplitude-reduction to the second (S2) relative to the first (S1) of identical brief auditory stimuli. This reduction is often mentioned in connection with the inability to filter redundant sensory stimuli typically manifested as inability to gate neuronal responses related to the P50 wave.[1, 2] The key neuronal structure responsible for the sensory gating process is the hippocampus. Inhibition of redundant stimuli in the hippocampus is affected via the release of glutamate from excitatory pathways, which is controlled by GABAB receptors. It is closely connected with a physiological deficit of hippocampal GABAergic interneurons, which demonstrates neuropathological changes in schizophrenia. Several drugs are able to improve sensory gating, the effect of which is explained by their ability to disinhibit GABAergic neurons in the hippocampus. The effect of setrons may be an example of such effective gabaergic interneurons disinhibition. This antagonist of 5-HT3 receptors increased (by disinhibition of GABAergic interneurons) release of acetylcholine, which by agonism of alpha7 nicotinic receptors improved auditory gating.[3] Besides the hippocampus the prefrontal cortex is an important neuronal part of the sensory gating. Patients with a prefrontal damage fail to suppress irrelevant sensory information, which leads to increased neural noise and inability to inhibit task-irrelevant information during behavioral tasks requiring performance over a delay. Some of the P50 source analysis leads to the conclusion that while the temporal cortices are the main generator of the P50 component, the prefrontal cortex seems to be a main contributor to the process of sensory gating (P50 amplitude reduction).[4] As in the case of the hippocampus, there are drugs that improve sensory gating by acting on the prefrontal cortex. Clonidine acts as an agonist of α2A noradrenergic receptors and has a proven restorative effect on sensory gating. Stimulation of α2A noradrenergic receptors on PFC spines by clonidine leads to strengthening of network connectivity, increase in neuronal PFC firing, and thus improves PFC regulation of sensory gating.[5] The aim of our poster is to interlink a pharmacological profile of neuronal areas that are involved in the inhibition of P50 wave with clinical treatment of schizophrenia. We believe that the neuropharmacological aspects of P50 wave offer an interesting hypothesis relating mainly to the pharmacological augmentation strategies. Some of them are suggested and explained further in our poster communication.

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References
Dopamine under the influence of sunlight? Transitions in solar irradiation explaining attentional performance in DRD4 7R carriers.
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Background
Previous research suggests that high exposure to solar irradiation has a preventive effect on the development of attention-deficit/hyperactivity disorder (ADHD) [1]. Note that the Dopaminergic DRD4 receptor is involved in phototransduction in the retina. Interestingly, being a DRD4 7R carrier while being born in spring and summer has been demonstrated to result in a 2.8 higher likelihood of developing hyperkinetic disorder, equivalent to ADHD [2]. These findings suggested a possible gene X environment interaction between the DRD4 7R allele and season of birth. The current study focused on the influence of solar irradiation exposure around birth on adult attentional performance.

Methods
We used an RDoC approach focusing on “inattention” operationalized as false negative errors, i.e. missed targets, from two cognitive tasks; the auditory oddball task and the continuous performance task. DRD4 genotype was regarded a vulnerability to develop ADHD, i.e. high inattention. We specifically aimed to test hypotheses that we generated based on previous studies. We distinguished the solar irradiation at birth-month from the difference in the solar irradiation between the month after birth and the month of birth to further understand previous results. Data of 277 healthy adult participants were extracted from the Brain Resource International Database. This database contains data from multiple laboratories (New York, Rhode Island, Nijmegen, Sydney, and Adelaide) creating variability in solar irradiation data.

Results
Results showed an interaction between DRD4 genotype and transition in solar irradiation following birth on the number of inattention errors made (F(1, 269)=6.785, p=.010). More specifically, a one-way ANOVA for the DRD4 7R carrier group showed a significant difference between positive and negative transition in solar irradiation (1,86)=8.602, p=.004, d=-0.449), while data from participants lacking the DRD4 7R genotype did not differ.
Conclusions
These results provide evidence that factors around birth influence adult performance and may strengthen or weaken the risk to develop attention related problems once already genetically at risk. Results also further strengthen the hypothesis that a relationship between solar irradiation and ADHD exists, possibly mediated by the dopamine DRD4 receptor.

References
A pilot study of sucrose-induced effect in resting alpha asymmetry
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Background and aim
Prospective studies have linked sucrose consumption to weight gain and obesity, which are in turn associated with the development of a range of adverse health effects including diabetes and premature cardiovascular disease, both identified as leading causes of health loss in New Zealand and Europe. Recent work has also reported that there are cognitive deficits induced by elevated intake of sugars. There is the need to improve understanding of how the processes involved in the deterioration of cognitive functions and mechanisms are modulated by the sucrose. The present study was to investigate the effect of sucrose on resting EEG alpha asymmetry using EEG.

Methods
We recorded resting, spontaneous EEG from 64 scalp electrodes according to the international 10/20 system (NeuroScan, A/D rate: 1000 Hz) while healthy volunteers (N=10) were orally administered sucrose (with 1% sweetness) and placebo solutions. The participants held these solutions in their mouth, still with eyes closed. EEG spectral indices from the left and right frontal (F3, F4), central (C4, C3) and posterior regions (P4, P3) of the scalp were extracted by a continuous wavelet transform and normalised into spectral distribution in the alpha (8-12 Hz) band. Sucrose-induced change in alpha asymmetry was analysed using ANOVA, with conditions (sucrose, placebo), hemisphere (left, right) and regions (frontal, central and posterior) as the within-subjects factors.

Results
Our results showed that there was no significant condition* hemisphere effect. However; a medium effect size (r= 0.33) may indicate some effect which did not turn out to be significant due to the limited sample size. A tendency for a reduced asymmetry value (i.e. F4-F3) was observed when the group was exposed to sucrose.

Discussion
Our findings provide preliminary evidence of sucrose-induced change in brain activity.
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