3rd Burghölzli Psychiatry Meeting

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(Foto Jan Conradi)

Abstracts

A)

Cellular and Molecular Psychiatry: Systems Biology, Animal Models, Genetics

1A)

***Reduced Inhibition and Excitation underlies circuit-wide changes in vivo
in Rett Syndrome***

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Introduction
Balance of excitation and inhibition (E/I) plays a key role in refining neural circuit development and plasticity and is disrupted in many neurodevelopmental disorders. Rett syndrome (RTT) arises from loss of function mutations in Mecp2 in the brain. The functional effects of MeCP2 on synaptic E/I and circuit-level computations, and the role of MeCP2 in inhibitory neuronal subtypes, especially Parvalbumin (PV+) and Somatostatin (SOM+)-expressing interneurons that play an important role in shaping circuit plasticity and E/I balance, are unresolved.

Methods
We used in vivo two-photon guided cell-attached and whole-cell patch-clamp recordings and awake Ca2+ imaging from cell-type specific conditional and global MeCP2 mutant mice. Age-matched MeCP2 wild-type littermate animals and Floxed-MeCP2 mice served as control.

Results
By analysing visual cortical responses in vivo, we show that visually-evoked excitatory and inhibitory conductances are both reduced in pyramidal neurons. Deletion of MeCP2 from PV+ and SOM+ expressing inhibitory interneurons reduces their responses and selectivity. PV-specific deletion substantially recapitulates effects of global MeCP2 deletion, by differentially reducing response levels, reliability and selectivity of pyramidal neurons. Interestingly, MeCP2 deletion also results in defective KCC expression leading to chloride (Cl-) imbalance, further impacting the effectiveness of GABAergic inhibition. Administration of human recombinant IGF1 (rhIGF1) cell-type specifically restores PV+ responses and increases KCC2 expression to correct the polarity of GABAergic inhibition.

Discussion
Loss of MeCP2 from specific interneuron types, and especially PV+ neurons, contributes crucially to the cell-specific and circuit-wide deficits of RTT, suggesting that such neurons have a pivotal role in the functional deficits that characterize the disorder. It also demonstrates a cell-type specific and mechanism-based therapeutic role for rhIGF1 in treating RTT.

2A)

D-amino acid oxidase (DAO) and DAO activator (DAOA)/G72 polymorphisms in individuals at-risk for psychosis

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Introduction
D-amino acid oxidase (DAO) and DAO activator (DAOA)/G72 polymorphisms have been described to be associated with schizophrenia. N-methyl-D-aspartate receptor hypofunction theory proposed in schizophrenia suggests DAOA binds to DAO, increases DAO activity leading to decreased D-serine, a co-agonist of NMDA receptor.

Methods
In a longitudinal cohort of 218 individuals at high risk (HR), ultra-high risk (UHR) for psychosis and non-HR/UHR group (n=33) (age:13-35 years), we assessed DAO (rs3918347, rs4623951) and DAOA (rs778293, rs3916971, rs746187) single nucleotide polymorphisms (SNP) for their association with transition to psychosis/schizophrenia.

Results/ Discussion
DAO and DAOA SNP frequencies did not significantly differ between converters to schizophrenia spectrum disorders (n=27) at 3-year follow-up and non-converters (n=65). In individuals meeting the UHR status of attenuated positive symptoms syndrome (APSS) (n=98) versus all other help-seeking individuals (n=90), the schizophrenia risk G-allele of DAO rs3918347 was found to be a risk for APSS (odd's ratio (OR)=1.846, 95% confidence interval (CI)=1.128-3.019, p=0.0193). We found a significant difference between APSS (n=98) versus non-HR/UHR group (n=33) (OR=0.35, 95% CI=0.12-1.02, p=0.05), and APSS+cognitive disturbances (COGDIS) (n=62) versus non-HR/UHR group (n=33) (OR=0.33, 95% CI=0.11-1.02, p=0.06) in DAOA rs3916971 dominant model (TT+TC, CC) which is in line with SZGene meta-analysis that showed T-allele to be protective variation for schizophrenia. Our findings suggest that DAO and DAOA polymorphisms might play a role in the pathogenesis of HR and UHR for psychosis. However, studies with larger cohorts and longer follow-ups are needed to confirm the role of DAO and DAOA genes in individuals at risk for psychosis/schizophrenia.

3A)

Transgenerational Transmission and Modification of Behavioral Deficits Induced by Prenatal Immune Activation

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Introduction
Maternal exposure to inflammatory insults during pregnancy increases the offspring's risk to develop neuropsychiatric disorders. It remains unknown, however, whether the increase in disease susceptibility induced by prenatal immune challenges could be transmitted across subsequent generations. The present study is the first to examine possible transgenerational effects using a well-established model of maternal viral-like immune activation in mice.

Methods
Pregnant mice (F0) were injected with the viral mimetic poly(I:C) (5 mg/kg, i.v.) or control solution in early pregnancy (gestation day 9). Upon reaching adulthood, F1 offspring were either allocated to behavioral testing or breeding, the latter of which served to produce subsequent (F2 and F3) generations of poly(I:C)-exposed or control ancestors. We then performed behavioral testing and genome-wide transcriptional profiling in adult offspring.

Results
Deficits in social interaction and cued fear, both of which emerge in F1 poly(I:C) offspring, are also present in the F2 and F3 generation. Behavioral despair, however, emerged as a novel phenotype in the F2 and F3 poly(I:C) generation. Transcriptomic analyses revealed a substantial number of differentially expressed genes in F1 and F2 poly(I:C) offspring relative to F1 and F2 controls. A remarkable number of genes (1132) were differentially expressed in both generations.

Discussion
Our findings demonstrate that behavioral deficits induced by prenatal infection can be transmitted and modified across subsequent generations. Future experiments will examine the possibility that the behavioral abnormalities and the differences in gene expression following prenatal immune activation are transmitted to subsequent generations via modifications in the epigenetic machinery.

4A)

The fruit of Rosa abyssinica Lindley (Rosaceae) is claimed to alleviate depression in folkloric Ethiopian medicine. Nevertheless, the antidepressant-like effect has not been assessed in rodent models of depression.

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Introduction
The fruit of Rosa abyssinica Lindley (Rosaceae) is claimed to alleviate depression in folkloric Ethiopian medicine. Nevertheless, the antidepressant-like effect has not been assessed in rodent models of depression.

Methods
The test animals were randomly selected and divided into five groups (n = 8). Group I and II received 2% Tween 80 and the standard drug imipramine (30 mg/kg) respectively while Groups III to V received increasing doses of the extracts and duration of immobility at three dose levels of the crude extract and (100, 200, and 400 mg/kg) was the parameter determined to assess the antidepressant-like activity of R. abyssinica in tail suspension test (TST) and forced swimming test (FST). The locomotor activity was also evaluated in terms of number of square crossings using the open field test (OFT) in order to rule out possible psycho-stimulant activity.

Results
The crude extract at the doses of 200 mg/kg and 400 mg/kg significantly reduced the time of immobility in the TST and FST. The aqueous fraction at 200 mg/kg displayed a significant reduction of 38% in the duration of immobility in TST which was superior to the effect of imipramine. The methanol fraction displayed a significant reduction in the duration of immobility of 33.93% only at 200 mg/kg. The ethyl acetate fraction was devoid of activity. No significant change in locomotor activity was detected in all the doses of the crude extract and imipramine in OFT.Discussion
We could demonstrate that the higher doses of SB and CGS clearly inhibit cell proliferation, indicating that these substances are toxic to the cells. What exactly the cause of this toxicity is, and whether it also affects gene expression levels or posttranslational modifications has to be further investigated.

Conclusion
The results of this study suggest that this plant possesses an appreciable antidepressant-like activity.

5A)

Mouse chronic social stress induces peripheral and CNS inflammation, dopamine deregulation and disrupted reward processing

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Introduction

Stressful life events are risk factors for depression. Stress induces, and depression is associated with, immune activation. Core depression symptoms, most notably decreased motivation, are proposed to stem from dopamine (DA) dysfunction. Whilst it is proposed that DA dysfunction can result from immune activation, the evidence for this is currently sparse. The aims of the present study were to investigate effects of social stress on: (1) Immune function in periphery and brain at cellular and molecular levels. (2) Mesolimbic DA pathway function. (3) Reward-directed behaviour using operant tasks.

Method

Mice were exposed to chronic social defeat (CSD), and the effects on the immune system, DA transmission and reward behaviour were assessed. Immune system activation was measured in spleen, liver and brain. DA changes were investigated in the ventral tegmental area (VTA) and nucleus accumbens (NAcc). Progressive ratio schedule (PRS) was used to assess CSD effects on reward-directed behaviour.

Results

Relative to controls, CSD mice exhibited increased spleen levels of granulocytes, inflammatory monocytes and T helper 17 cells, increased plasma levels of iNOS, and increased liver expression levels of genes for kynurenine-pathway enzymes. Microglia activation was increased in the VTA, and dopamine turnover (DOPAC/DA) was decreased in NAcc. When challenged with a DA reuptake inhibitor, CSD mice exhibited both attenuated hyper-locomotion and NAcc *c-Fos* activation. In operant tests with sucrose-pellet reinforcement, CSD mice exhibited decreased motivation under effortful conditions.

Discussion

This study provides evidence in support of the hypothesis that stress-induced peripheral and brain inflammation co-occur with attenuated mesolimbic DA function including decreased interest in reward. This model will be utilised to identify novel targets for restoring DA function as an antidepressant treatment.

6A)

From maltreated children to psychopathic adults – The role of the monoamine oxidase A gene

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Introduction
Psychopaths typically show affective deficits, manipulative skills, a deviant lifestyle, and antisocial behaviour. Regarding etiological factors of this severe personality disorder, gene x environment effects have moved into focus. Some studies have shown that a low activity polymorphism of the monoamine oxidase A (MAOA-A) gene interacts with childhood maltreatment to predict antisocial behaviour, whereas a high activity variant does not. However, little research has so far been done on the whole spectrum of psychopathic features apart from the antisocial factor.

Method
We used a community sample of 1527 men and 2370 women from the Genetics of Sexuality and Aggression project, a large-scale population-based survey among adult twins and their siblings from Finland. Based on information on childhood maltreatment, psychopathic traits, and genotype, we estimated structural equation models for women and men separately. The genotype served as the grouping variable to check for possible differences between carriers of the low and high activity variants.

Results
Carriers of the two respective polymorphisms did not differ in their mean scores on the maltreatment and psychopathy measures. Moreover, there were no significant between-group differences regarding the regression of psychopathy on maltreatment.

Discussion
The results suggest that psychopathy cannot be predicted by an interaction between maltreatment and the low activity variant of the MAO-A gene. Further research should examine the role of other genes, such as the serotonin transporter gene, to shed light on the complex molecular biological processes that contribute to the development of psychopathic features.

7A)

Gene x environment evidence for amygdala oligodendrocyte mediation of stress-induced emotional pathologies

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Identification of the CNS cellular changes that mediate stress-induced emotional disorders is essential. Oligodendrocytes and myelination underlie neurocircuitry and connectivity. In depression, oligodendrocyte gene and protein-marker expression is reduced, including in amygdala. In mice, chronic social defeat (CSD) stress resulted in reduced amygdala expression of a number of oligodendrocyte-specific genes, as identified using RNA-seq transcriptomics. Cell deconvolution analysis indicated a decrease in the proportion of amygdala oligodendrocytes relative to other cell types in CSD mice. Using fMRI, connectivity was increased between amygdala and frontal cortex in CSD mice. A knockout mouse for the oligodendrocyte gene, cyclic nucleotide phosphodiesterase, was studied in a 2 genotype (G) (WT, Cnp+/-) x 2 environment (E) (CSD, Control) design, in terms of emotional behaviour and CNS inflammation. In a social motivation test, there was a GxE interaction effect, with CSD reducing social motivation in Cnp+/- mice specifically. In Pavlovian fear conditioning, Cnp+/- decreased fear expression and CSD increased fear expression in Cnp+/- and WT. Using Iba-1 immunohistochemistry as a marker of microglia activation, there was a GxE additive effect in amygdala, with expression lowest in WTxCON and highest in Cnp+/-xCSD. This mouse model provides ExG and GxE evidence for the involvement of inhibited functioning of amygdala oligodendroyctes in the mediation of stress-induced emotional pathologies.

8A)

Longitudinal opto-fMRI of serotonergic function in mice undergoing SSRI treatment

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Introduction

Serotonergic system changes are widely implicated in affective disorders. Selective Serotonin Reuptake Inhibitors (SSRIs) are the foremost drug class for treating depression, and find significant use in treating anxiety, phobia and other disorders. To date there exists no unbiased whole-brain representation of serotonergic neurotransmission strength, and no protocol to longitudinally study treatment and/or drug effects at the whole-brain level. Herein we present an opto-fMRI protocol which provides these capabilities, and describe preliminary results of chronic SSRI treatment in mice.

Method

The Dorsal Raphe (DR) of C57BL/6 mice was optogenetically targeted, and mice were imaged with the same optical stimulation protocol on 5 occasions: before, during acute, chronic (2x), and after fluoxetine treatment. The data were analysed with a GLM to obtain per-session main group effects. Behavioural data was acquired on a separate cohort.

Results

Behavioural assays indicate our protocol can induce antidepressive effects in healthy mice. GLM results show DR activation and forebrain deactivation, with a heterogeneous profile across measurement sessions. The maximum potentiation of activation and deactivation occurs after 4 weeks of chronic Fluoxetine administration.

Discussion

Our protocol is shown as feasible for longitudinal, whole-brain, functional serotonergic system imaging and for the study of psychoactive drugs. GLM results present an interesting concordance with the clinical activity profile of fluoxetine, but we acknowledge the high variance in our data, and detail possible explanations.

B)

Theoretical Psychiatry: Behavioral Models, Computational approaches, humanities

1B)

Neuromodulatory influences on prediction error signaling in reward learning: A computational trial-by-trial EEG analysis

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Introduction
Adaptive behaviour in volatile environments requires updating beliefs about the probabilistic structure of the environment; this, in turn, draws on hierarchically related prediction errors (PEs). The PEs may be reflected by dopaminergic and cholinergic signalling; this is a central pathophysiological theme in schizophrenia. Here, we investigated drug effects on the timing of PEs, using computational trial-by-trial EEG analyses.

Methods
68 healthy male volunteers were tested using EEG while performing a reward associative learning task under amisulpride/biperiden/placebo. Having determined an optimal model for behavioral data, computational trajectories of low-level choice PE (c 1; reward outcome), high-level PE (2; probability of outcome) and the respective precision-weights were used as covariates in single-subject trial-by-trial GLM analyses. The resulting parameter estimates entered one-sample t-tests (group-level) at the sensor level.

Results
A three-level Hierarchical Gaussian Filter (HGF) with fixed k best explained the data and was used to compute the computational regressors for EEG analyses. We found a significant correlation between the EEG signal and the
- low-level PE ($c\delta_1$) at 92ms after outcome onset,
- low-level precision-weight at 138ms,
- high-level PE (δ_2) at 208ms,
- high-level precision-weight at 264ms.
Furthermore, amisulpride modulated the electrophysiological expression of the high-level precision-weight, at 274 and 282 ms after trial outcome.

Discussion
We found that the temporal expression of hierarchical PEs and their precisions in EEG activity was consistent with the computational hierarchy postulated by the HGF. Amisulpride affected the representation of high-level precision, suggesting a role of dopamine in encoding certainty about stability of environmental structure.

2B)

Trajectory estimation of clinical marker for prediction of relapse in major depressive disorder

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Introduction

We investigate relapse after successful treatment with antidepressant medication using data from the STAR*D study (Rush et al 2006), the biggest prospective study on treatment in depression to date. In this study, patients were treated for a period of 12-14 weeks, after which they were followed up for one year. Our aim was to predict the time course of QIDS scores, which are employed as an index for depression. Based on these predicted time courses, we aimed to predict if a participant would relapse within a year after successful treatment.

Methods

Treatment decisions are usually predicated on predictions about the future course of an illness, but few tools exist that can predict disease trajectories beyond simple linear or quadratic trends. We propose an extension to multiple sequential linear regression for prediction of individual non-linear time courses of a clinical marker based on cross-sectional baseline data. The method implicitly assumes that each baseline feature's influence on the clinical marker changes in time, resulting in the estimation of (non-observed) feature influence trajectories. This is based on a kernel method called Gaussian process regression (Williams and Rasmussen 2006). The time course of the marker then arises as a linear combination of these influence trajectories. Further, the new method can easily deal with missing observations, missing features, and unequally spaced measurement time points.

Results

Of the 4041 participants that were enrolled in the study, we had to exclude many since they did not complete the treatment or did not show up for follow up assessments. We used a total of 610 patients for our analyses. By thresholding the predicted QIDS trajectories such that we obtained a binary prediction relapse / no-relapse, we could predict relapse with a balanced accuracy of 64.2 percent. This is similar to prediction accuracy of remission prior to treatment by Chekroud et al 2016; for prediction of relapse, we did not find any other analysis of the same order of magnitude with respect to patients. We show that our method currently still overfits, such that there is further room for improvement. Finally, we aim to apply the method to an ongoing study at our own institute, once data collection is finished.

References

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3B)

Modelling fear conditioned bradycardia and respiratory amplitude in humans

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Introduction
Cued fear conditioning is an experimental paradigm commonly used to investigate aversive Pavlovian learning. While fear-conditioned stimuli (CS+) elicit overt behaviour in many mammals, this is not the case in humans. In contrast, autonomic activity is used to quantify fear learning in humans, typically measured by skin conductance responses (SCR). Here, we investigate whether heart period responses (HPR) and respiratory amplitude responses (RAR) are suitable alternative measures of fear learning in humans.

Methods
In total, we analyse six datasets involving delay and trace conditioning, including a dataset acquired during MRI scanning. After establishing that both the heart period and the respiratory amplitude respond differently to CS+ and CS-, we develop a psychophysiological model of the fear-conditioned response from both modalities that regards interpolated HPR and RAR time series as the output of a linear time invariant system. These models are inverted to yield estimates of autonomic input into the cardiac and the respiratory system.

Results
In both modalities, we show that the sensitivity to distinguish CS+ and CS- is higher for model-based estimates than standard model-free (e.g., peak scoring) analyses. Finally, we compare the performance of the best model-based implementation of these modalities to the one from SCR, obtaining that HPR significantly outperforms both SCR and RAR, which in turn perform similarly.

Discussion
Overall, our work provides two novel and robust tools to investigate fear memory in humans that may allow wide and straightforward applicability to diverse experimental contexts.

4B)

COMPASS: Comparing Brain Activity Across Patients With Differential Treatment Response In Schizophrenia — an observational study.

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Introduction

To date, the selection of antipsychotic treatment for patients with a psychotic disorder is almost entirely lead by the history of treatment with particular antipsychotic drugs or anticipated side–effects. The aim of this study is to identify subgroups of patients which benefit from a particular antipsychotic treatment and to predict the treatment response.

Methods

We aim to recruit n = 240 patients with schizophrenia and related disorders with an established antipsychotic treatment prior to a switch to/augmentation with Clozapine or Olanzapine, which share a similar pharmacological profile when compared to most other 2nd generation antipsychotics. After a clinical assessment, participants undergo an EEG (working memory, associative learning under volatility, auditory MMN) and an optional MRI (fMRI: auditory MMN, rest; sMRI: T1, T2, DWI). Blood samples will be collected (genetics and inflammation parameters). After 2 and 8 weeks of treatment with Clozapine/Olanzapine a clinical follow-up will be conducted. The study is observational, thus, the decision of changing the antipsychotic treatment is not influenced.

Results

Using computational models to analyse the neurophysiological and structural data we hope to infer on the properties of the cholinergic, dopaminergic, and glutamatergic systems and to be able to predict treatment response to a particular pharmacological profile. Analyses will be informed by the genetic, inflammatory as well as clinical parameters.

Discussion

If successful, this proof of concept study will have a significant impact on the treatment of psychotic disorders and will help to reduce the burden, the duration of treatment and eventually health care cost. However, prospective studies will be needed to verify and refine the clinical usability.

5B)

The computational and neurochemical bases of premature responding impulsivity in humans

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Introduction

Premature responding, or waiting impulsivity, has been proposed as a common behavioural thread linking the symptomatology of multiple neuropsychiatric disorders, such as addictions, psychosis and ADHD. Moreover, this impulsivity sub-type appears to exhibit an unusually clear neurochemical basis, with dopamine and serotonin systems having distinct effects on the behaviour. However, the neurophysiological mechanisms underlying these phenomena remain under-researched in humans.

Methods

We administered a novel decision-making paradigm during BOLD fMRI data acquisition in healthy humans, in independent studies with (n = 50) and without (n = 24) a placebo-controlled, selective serotonin reuptake inhibitor. We used hierarchical Bayesian modelling of behavior and a computational neuroimaging approach to investigate the neural bases of waiting impulsivity under uncertainty in a probabilistic learning environment.

Results

During decision-making, a dynamic, model-based measure of waiting impulsivity was found to be significantly associated with BOLD activation in a network including anterior insula and midbrain regions. Moreover, during decision feedback, belief-updating 'prediction error' signals were associated with activation in striatum and fronto-parietal cortical regions. Finally, we found a significant association between model-based measures of premature responding and an established questionnaire-based measure of impulsivity.

Discussion

Our findings identify behavioural and neural correlates of a formal construct of premature responding impulsivity under uncertainty. We observe BOLD fMRI activations associated with our computational measures of impulsivity and prediction error in cortical and subcortical regions known to be key parts of the serotonin and dopamine pathways and to underpin a variety of behaviours relevant for impulsivity and related disorders in humans.

C)

Neuroimaging: MRI, PET, NIRS, Spectroscopy, EEG, MEG

1C)

Informing participants about the study purpose affects resting state fMRI connectivity

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Introduction

Resting state functional magnetic resonance imaging (rsfMRI) is a widely used technique to investigate task-unrelated brain networks. Yet, even in rsfMRI studies there is considerable variation regarding study purpose and instruction, which might affect neuronal sources linked to the brain's resting state, possibly compromising the comparability of different studies on the same topic. The objective of the present study was therefore to systematically investigate the influence of providing information on the study purpose on static and dynamic resting-state functional connectivity (rs-FC).

Methods

Thirty right-handed healthy elderly volunteers (61-80 years) were scanned during an eyes-closed rsfMRI run. One group was informed about a particular study aim ("we study an important brain function") immediately before the rsfMRI run, whereas the other group was not informed. Data were analyzed using the CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012) and GIFT toolboxes (Cichocki et al., 2003; Allen et al., 2012). Static regional analysis (i.e., Brodmann areas) as well as network-specific rs-FC using independent component analysis (ICA) and dynamic rs-FC was performed.

Results

Static regional analysis showed between-group differences in several Brodmann areas (BA 8-11, 17, 20, 44-45, $p < 0.05$, corrected). Using a group ICA analysis, participants of the group informed after scanning revealed higher rs-FC of the medial prefrontal and anterior cingulate cortex component, whose connectivity to the left central executive network was increased in dynamic rs-FC ($p < 0.05$, corrected).

Conclusions

Our results suggest that subject information prior to rsfMRI should be taken into consideration when comparing rs-FC findings between existing studies.

2C)

Electroencephalogram connectivity in frontal networks to predict outcome of electroconvulsive therapy in major depressive disorder

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Introduction
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.

3C)

Perception of negative and positive emotional stimuli and SSRI treatment outcome in major depressive disorder –a preliminary fMRI study

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Introduction
Clinically useful predictors of treatment outcome in major depressive disorder (MDD) are needed. There is preliminary and not yet sufficiently consistent evidence that neural activity could serve as biomarker for response to different treatment approaches. We here wanted to investigate the prediction of response to treatment with selective serotonin reuptake inhibitor (SSRI) in MDD.

Methods
We examined the association between functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) response during the perception of negative and positive emotional stimuli compared to neutral stimuli prior to treatment and outcome after 6 weeks of treatment with the selective serotonin reuptake inhibitor (SSRI) escitalopram in 20 patients with MDD. We compared brain activation in responders (>50% BDI improvement) to non-responders at the whole-brain level. Activity in resulting clusters was correlated with BDI change (pre to post treatment). FMRI-analysis was carried out using BrainVoyager QX 2.8 (Braininnovation, NL).

Results
While perceiving positive stimuli, responders were characterized by stronger pre-treatment activation in the posterior cingulate cortex (PCC), as well as the right hippocampus. (HC) During both the perception of positive and negative stimuli, responders also showed stronger pre-treatment activation in the anterior medial prefrontal cortex (amPFC). Brain activation in these regions was positively correlated with reduction in BDI Brain activation in these regions was positively correlated with the BDI change. In addition, severity of pre-treatment depression (BDI) was negatively correlated with subjective valence.

Discussion
This study supports the hypothesis that pre-treatment activity of distinct brain regions may be correlated with SSRI treatment outcome and may thus serve as treatment response predictor.

4C)

Huntington's Disease and EEG Microstates

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Huntington's disease (HD) is an inherited progressive brain disorder leading to severe neurologic, psychiatric and cognitive symptoms. The brain-electric processing steps affected by the disease were studied using an EEG microstate analysis. 3 minutes of vigilance-controlled 19-channel EEG was recorded from 20 un-medicated HD patients (clinical stages 1 to 3) and from 20 age and gender matched healthy controls. The EEG data were cleaned from artifacts, FFT-filtered from 2-20 Hz and re-referenced to the average reference. The microstate analysis identifies classes of quasi-stable potential distributions on the scalp and computes the mean occurrence, duration and coverage for the microstates of each class.

Four classes of microstates were extracted and labelled A, B, C and D based on their similarity to published normative classes. Microstate parameter comparisons between groups used manovas and post-hoc t-tests. HD patients showed an abnormally high coverage ($p<0.05$) and duration ($p<0.10$) of microstates of classes A and B and abnormal decreases for C and D for coverage ($p<0.10$ for C and $p<0.05$ for D) and occurrence ($p<0.05$). The results mirror the complex symptomatology of HD as all microstate classes were affected. The parameter decreases of classes C and D possibly indicate a disturbed subjective own body representation and reduced reality testing in patients. While the functional significance of the parameter increases in class B is still unclear, the increase in class A might be related to symptoms of anxiety or could be a predictor for psychotic symptoms.

5C)

Persistency of dynamic brain connectivity relates to memory decline and local iron in cognitively normal elderly subjects

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Introduction
Clinical manifestation of Alzheimer's disease (AD) is characterised by progressive memory decline in the elderly. While the risk for cognitive decline due to AD is linked to the concurrent abundance of beta-Amyloid (Aß) and other neurodegenerative brain alterations, little is known on involved neural mechanisms.

Methods
37 cognitively normal elderly subjects (age: 74 (6.0), MMSE: 29.0 (1.1)) were investigated by 11C Pittsburgh Compound-B Positron Emission Tomography (PiB-PET) for cortical Aß. Brain iron load was inferred from quantitative-susceptibility-mapping (QSM) MRI at high field-strength of 7 Tesla (7T). Resting-state T2prep BOLD-functional MRI at 7T was measured to infer network occurrence of dynamic brain networks and investigate relationships with cognitive decline over two years, local Aß and iron.

Results
Declined memory was associated with an anterior-posterior network (Hotelling's T2 test: $p>0.008$) and iron load at network-nodes located at left precuneus and right caudate nucleus (MANOVA:$p<0.022$, FDR-corrected). No significant effect was found for Aß (MANOVA: $p>0.1$). In addition those with APOE-e4 carrier status and episodic memory decline had increased occurrence of a frontal and occipito-temporal network and decreased occurrence of a fronto-temporal network.

Discussion
Our data indicate an association between declined memory performance and network occurrence of an anterior-posterior dynamic network in cognitively normal elderly subjects. The association of major nodes with increased iron load may indicate neurodegenerative brain change during aging and may thus be consistent with earlier reports on tau in AD.

6C)

Novel insights into neurometabolic mechanisms of cocaine addiction: Reduced glutamate levels in the nucleus accumbens

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Introduction
Animal studies show that chronic cocaine use leads to decreased glutamate levels in the nucleus accumbens (NAcc), whereas drug-seeking reinstatement is accompanied by enhanced glutamatergic transmission1. However, little is known about such neurometabolic alterations in humans. We thus aim to investigate changes of the glutamate homeostasis in the NAcc of cocaine dependent individuals by means of a novel proton magnetic resonance spectroscopy (1H-MRS) protocol that we have recently developed.

Methods
In 16 cocaine dependent individuals (CD) and 22 healthy controls (HC), non-water suppressed PRESS localization 1H-MRS preceded by a metabolite-cycling pulse combined with inner-volume saturation was performed on a 3T Philips Achieva System. MRS spectra were obtained from a voxel of 9.4x18.8x8.4mm, covering the anatomical dimensions of the left NAcc. For absolute quantification of the metabolites, a method based on the principle of reciprocity has been applied.

Results
An average signal-to-noise ratio of 16.97 and a mean line width of 6.93Hz (in single spectra) indicate good spectral quality. Metabolite concentrations of interest were quantified reliably using LCModel4 with Cramér-Rao lower bounds<10%. Moreover, glutamate concentrations in CDs (M=0.011, SD=0.001) were significantly reduced compared to HCs (M=0.013, SD=0.002), $t(34)=3.81$, $p=.001$, $d=1.20$.

Discussion
Despite the small voxel size, this novel ^{1}H-MRS protocol achieves high data quality and, thus, finally allows a reliable detection of glutamate in the human NAcc. For the first time this reveals that, in accordance with animal models, glutamatergic alterations occur in cocaine dependent humans and might play a decisive role in the development and maintenance of cocaine dependence.

7C)

Neural initialization of audiovisual integration in prereaders at varying risk for developmental dyslexia

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Introduction
Learning letter-speech sound correspondences is a major step in reading acquisition and is severely impaired in children with dyslexia. Up to now, it remains largely unknown how quickly neural networks adopt specific functions during audiovisual integration of linguistic information when prereading children learn letter-speech sound correspondences.

Methods
Here, we simulated the process of learning letter-speech sound correspondences in 20 prereading children (6.13-7.17 years) at varying risk for dyslexia by training artificial letter-speech sound correspondences within a single experimental session. Subsequently, we acquired simultaneously event-related potentials (ERP) and functional magnetic resonance imaging (fMRI) scans during implicit audiovisual presentation of trained and untrained pairs.

Results
Audiovisual integration of trained pairs correlated with individual learning rates in right superior temporal, left inferior temporal, and bilateral parietal areas and with phonological awareness in left temporal areas. In correspondence, a differential left-lateralized parietooccipitotemporal ERP at 400 ms for trained pairs correlated with learning achievement and familial risk. Finally, a late (650 ms) posterior negativity indicating audiovisual congruency of trained pairs was associated with increased fMRI activation in the left occipital cortex.

Discussion
Taken together, a short (<30 min) letter-speech sound training initializes audiovisual integration in neural systems that are responsible for processing linguistic information in proficient readers. To conclude, the ability to learn grapheme-phoneme correspondences, the familial history of reading disability, and phonological awareness of prereading children account for the degree of audiovisual integration in a distributed brain network. Such findings on emerging linguistic audiovisual integration could allow for distinguishing between children with typical and atypical reading development.

8C)

Training channels visual specialization for print in prereaders: Neural evidence from EEG and fMRI

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Introduction
Fully automated visual processing of print is an important prerequisite for reading, but the development of acquiring this expertise remains elusive. In the present study, we examined how prereading children process visual print information on different stages of emerging expertise.

Methods
In a simultaneous electroencephalography (EEG)/functional magnetic resonance imaging (fMRI) study children were presented with four different character types ranging from highly familiar to completely novel (Arabic digits, Latin letters, trained false fonts and untrained false fonts).

Results
Our data showed expertise dependent activation differences for the visual event-related potential (ERP) N1 and for ventral occipito-temporal (vOT) fMRI activations. For the first time, we show a significant modulation of visual character processing in the brains of prereaders after short character-speech sound training (<30min). This emerging visual specialization was reflected in a more pronounced activation for trained compared to untrained false fonts irrespective of modality and a strong relation between fast learning and activation in the left vOT.

Discussion
These results are directly linked to the interactive specialization model, which explains visual expertise through an interaction of feedback and feedforward information during early learning stages. Moreover, our data imply that training channels visual specialization for print in prereaders dependent on training success. Hence, our results critically extend the knowledge of neural changes in the very initial stage of visual specialization in the context of reading acquisition.

9C)

Increased reaction to monetary rewards in female fibromyalgia patients with and without depression: a [11C]raclopride bolus-plus-infusion PET study

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Introduction

Patients with fibromyalgia syndrome (FMS) experience widespread pain, and comorbid depressive disorder is common. The pathophysiology of FMS has not been fully elucidated, and it remains difficult to treat. Reduced mesolimbic dopamine function and responses to reward occur in patients with depression, and chronic pain may also impair reward processing. We hypothesized that abnormal dopamine responses to rewards are associated with both FMS and comorbid depression.

Method

Twenty-four women with FMS (11 with comorbid depression) and 17 healthy controls underwent positron emission tomography with [11C]raclopride. The primary outcome was differing regional D2/3 receptor binding potentials resulting from an unpredictable reward condition or a sensorimotor control condition.

Results

There were significant reductions in D2/3 receptor binding potentials in the reward vs. the control condition in the right nucleus accumbens and caudate nucleus, which may indicate increased dopamine release. The effects in the right nucleus accumbens were more prominent in patients with FMS and comorbid depression (41.1%) compared to healthy controls (23.3%; $p < 0.01$). Reductions in the right caudate nucleus of patients with FMS were also greater in patients with comorbid depression (24.6%) compared to patients without depression (13.4%; $p < 0.02$).

Conclusions

These results contribute to understanding of depression associated with chronic pain conditions and have clinical relevance to treatment options for patients with FMS, based on whether depression is a comorbid condition. Treatment should include consideration of depressive symptoms when they are present and dopamine functioning should be targeted in patients without depression.

10C)

Neuroanatomical changes associated with chronic cocaine consumption: A longitudinal MRI-Analysis

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Introduction
Cross-sectional studies have consistently shown that cocaine consumption is associated with altered brain structures mostly apparent as decreased gray matter (GM) volumes in regions of the prefrontal cortex and the insula. However, it is still unclear if these neuroanatomical alterations are caused by cocaine intake or if they represent predispositions for stimulant use and addiction. Thus, by applying a longitudinal study design we aim to analyze GM changes in cocaine users compared to controls.

Method
In the preliminary analyses 13 drug-naïve controls, 13 cocaine users with increased, and 13 cocaine users with decreased cocaine use were included. The groups were matched for age, gender, verbal IQ, and length of follow-up interval. Imaging data was processed using the longitudinal-pipeline of the FreeSurfer software suite. Linear mixed-effects models were used to analyze if there is any difference in the rate of change among the three groups in cortical thickness (CT), surface area (CSA), and volume (CV). The analysis was restricted to the frontal cortex and insula.

Results
Our preliminary results show significant group differences in the rate of change in CT, CSA, and CV in regions such as the rostral, caudal, and superior frontal gyrus and lateral orbitofrontal cortex.
Within all clusters post hoc analysis depict significant interactions of time and group for the increasers and controls. Cocaine decreasers and controls did not differ in neuroanatomical changes over time.

Conclusions
Our preliminary findings suggest that brain alterations found in cocaine users are at least in part driven by chronic cocaine intake.

11C)

Cerebral networks underlying hypersensitivity to salient sounds in posttraumatic stress disorder

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Introduction
The ability to accurately detect potentially meaningful environmental events is essential for survival. Patients with posttraumatic stress disorder (PTSD) are often overly sensitive and responsive to unexpected environmental stimuli, including those not related to the traumatic event or threat. We investigated whether hyperresponsiveness to brief sounds in the ventral attention network (VAN), which mediates stimulus-driven orienting, is accompanied by hyperresponsiveness in the auditory, salience, or dorsal attention networks (DAN) in PTSD.

Methods
PTSD (n = 29) and trauma-exposed healthy subjects (Non-PTSD, n = 25) passively listened to 500 msec, 95 dB sound pressure level pure tone or white noise bursts presented every 30 sec during concurrent psychophysiological and fMRI recording. After scanning, subjects evaluated the relative loudness and aversiveness of the sounds by magnitude estimation.

Results
We observed higher heart rate (on average 0.45 BPM, 95% CI [0.03, 0.87]) and neural activity responses (t's ≥ 4.00, p's ≤ 0.05, FWE-corrected) to white noise in temporoparietal junction (VAN) and intraparietal sulcus (DAN) in PTSD, compared to Non-PTSD, subjects. PTSD subjects tended to experience the sounds as more aversive (p = 0.090) than Non-PTSD subjects and made more errors in an attention task (p = 0.020).

Discussion
Hyperresponsiveness of the VAN to unexpected, salient sounds in PTSD may arise from atypical DAN influences, which typically focus activity in the VAN towards important events. Misattribution of the behavioral relevance of unexpected sounds, rather than sensory hypersensitivity or atypical salience attribution, may underlie hyper-responsiveness to irrelevant, trauma-unrelated auditory stimuli in PTSD.

12C)

Mesio-temporal theta oscillations in a human anxiety task

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Introduction
Theta oscillations in mesiotemporal structures have been proposed as a neural signature of anxiety models in rodents, which typically rely on conflicts between approach and avoidance. Recent work using magnetoencephalography (MEG) has shown that human hippocampal theta oscillations during approach/avoidance conflict relate to learned threat probabilities. Here, we extend these findings by recording local field potentials directly from subcortical structures in humans, using intracranial electroencephalography (iEEG).

Methods
We recorded iEEG from three patients with mesiotemporal epilepsy. Patients collected monetary tokens under threat of virtual predation. Probability of threat had to be learned by experience while monetary loss was explicitly signalled. Power spectra for theta oscillations (1-8 Hz) were extracted over 1 s windows and were statistically evaluated using independent sample t-tests, corrected for multiple comparisons with non-parameteric permutations.

Results
All patients showed a significant increase in the power of theta oscillations during 1 s following the token appearance, compared to a baseline period (p<0.05). Two patients had an additional increase in theta power during 1 s following the trial start. Only one patient could learn the threat probabilities and also showed higher theta power for higher threat level and higher theta power for higher potential loss. The later effect was partly replicated in the other two patients.

Discussion
Our findings confirm that approach-avoidance conflict increases mesiotemporal theta power in humans. They extend previous MEG results, by suggesting that mesiotemporal theta oscillations relate to expected loss, whether it is explicitly signalled or successfully learned.

13C)

The effect of dopaminergic neuromodulatory interventions on measured BOLD-signal: Implications for future fMRI studies in medicated patients

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Introduction
Functional magnetic resonance imaging (fMRI), i.e. assessing the blood oxygenated level-dependent (BOLD) signal, emerged as method to investigate brain function associated with mental disorders. Treatment of mental disorders is often based on dopaminergic neuromodulatory interventions, but their potential effects on the BOLD-signal have not been assessed in humans yet. Preclinical studies suggest strong influences of dopaminergic neuromodulators on neurovascular coupling which may alter fMRI results. The purpose of this study was to investigate the effect of pharmacological interventions in terms of dopamine-agonism and –antagonism on measured BOLD-signal in healthy volunteers.

Methods
Twenty-two healthy volunteers underwent three fMRI sessions at 3.0 Tesla. Before each session, participants received in a double-blind placebo-controlled cross-over design either a dopamine antagonist (100mg Quetiapine), dopamine agonist (0.25mg Pramipexol) or placebo. During each session, a checkerboard-paradigm (2s active blocks interleaved with 10s black screen; 10 repetitions) was presented. Data was preprocessed and BOLD signal in the primary visual cortex was estimated for each subject and run using SPM. Between-drug differences were tested statistically.

Results
Dopaminergic modulation had no effect on the timing of the BOLD-time course. Compared to placebo, volunteers showed increased BOLD-amplitudes after dopamine-antagonism and decreased BOLD-amplitudes after dopamine-agonism in the visual cortex.

Discussion
This is the first study to investigate the effect of dopaminergic modulation on measured BOLD signal in healthy volunteers. Alterations of the BOLD signal may be caused by modulation of energy (O2)-consumption. Presented results enable a better discrimination between medication-induced and actual alterations in studies investigating fMRI activity in medicated patients.

14C)

Gamma-hydroxybutyrate increases resting state limbic perfusion and body and emotion sensation in humans

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Gamma-hydroxybutyrate (GHB) is a putative neurotransmitter, a drug of abuse, and a medical treatment for narcolepsy and other neuropsychiatric disorders. The drug strongly influences subjective experiences and behaviours related to mood regulation, social interaction, sexual behaviour, and sleep-wake regulation. However, the neural mechanisms of these properties in humans are largely unknown. Aiming at identifying the neural signature of subjective and behavioral GHB effects, we performed a series of studies applying blood analyses, electroencephalography (EEG), and multimodal functional magnetic resonance imaging (fMRI) in healthy male volunteers.

In these studies, we demonstrated that GHB exerts a broad spectrum of subjective and behavioral properties, including sedation and stimulation at the same time, euphoria, enhanced emotion and body sensation, and prosocial as well as prosexual effects. These are mediated by an activation of the mesolimbic reward system including the nucleus accumbens, core limbic areas such as the anterior cingulate cortex (ACC) and the insula, and an increased recruitment of areas pertaining to the cognitive control network (CCN). Moreover, distinct neuroendocrine and electrophysiological alterations could be identified. Considering the industry withdrawal from psychopharmacology development, repurposing of drugs according to their behavioural and clinical profiles has gained increasing relevance. As such, GHB seems to be an attractive candidate as an experimental therapeutic in depression.

15C)

Ventral Striatal Dysfunction and Symptom Expression in Individuals with Schizotypal Personality Traits and Early Psychosis

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Introduction
Striatal abnormalities play a crucial role in the pathophysiology of schizophrenia. Growing evidence suggests an association between aberrant striatal activity during reward anticipation and symptom dimensions in schizophrenia. However, it is not clear whether this holds across the psychosis continuum. The aim of the present study was to investigate alterations of ventral striatal activation during reward anticipation and its relationship to symptom expression in persons with schizotypal personality traits and first-episode psychosis.

Methods
26 individuals with high schizotypal personality traits, 26 patients with non-affective first-episode psychosis (including 13 with brief psychotic disorder and 13 with first-episode schizophrenia) and 25 healthy controls underwent event-related functional magnetic resonance imaging while performing a variant of the monetary incentive delay task.

Results
Ventral striatal was positively correlated with total symptom severity, in particular the level of positive symptoms. This association was observed across the psychosis continuum and within each subgroup. Patients with first-episode schizophrenia showed the strongest elevation of striatal activation during reward anticipation, although symptom levels did not differ between groups in the psychosis continuum.

Discussion
While our results provide evidence that variance in striatal activation is mainly explained by dimensional symptom expression, patients with schizophrenia show an additional dysregulation of striatal activation. Trans-diagnostic approaches are promising in order to disentangle dimensional and categorical neural mechanisms in the psychosis continuum.

D)

Clinical Research: Aetiology, Epidemiology, Neuropsychology, Diagnostics

1D)

Mesial temporal lobe epilepsy (MTLE) is associated with deficits in recognition of emotional facial expressions.

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Introduction

Mesial temporal lobe epilepsy (MTLE) is associated with deficits in recognition of emotional facial expressions. Functional MRI studies show decreased activity of the amygdala but also further face processing regions during the perception of facial expressions. However, alterations of functional connectivity (FC) between the amygdalae and face processing regions in MTLE are still unknown.

Method

We examined 48 patients with unilateral epilepsy (16 left-MTLE, 17 right-MTLE, 15 extra-MTLE) and 30 healthy controls. Neural responses to dynamic fearful faces were measured in a block-design using fMRI. ROI-to-ROI FC was analyzed using the CONN functional connectivity toolbox.

Results

In healthy controls, an extensive network of cortical and subcortical regions showed positive FC during perception of fearful faces. A reduced network centered on the right amygdala was present in left MTLE. Right MTLE patients only showed FC among left periaqueductal gray and right anterior superior temporal sulcus.

Discussion

Our findings support assumptions of a right-hemispheric dominance for the processing of emotional faces. Its disruption might contribute to deficits in the recognition of facial expression in MTLE.

2D)

Patterns of Adverse Childhood Experiences in Juveniles Who Have Sexually Offended and Their Relations to Offense Characteristics and Criminal Recidivism

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Introduction
Adverse childhood experiences (ACE) have been suggested crucial factors in the aetiology of sexual offending in adolescents. Their role in predicting recidivism is, however, not yet elaborated. Because juveniles who have sexually offended (JSOs) are heterogeneous concerning ACEs and criminal characteristics (e.g., victim choice / violent behaviors), the present study aimed at (a) empirically deriving distinct JSO-subtypes based on their ACE-profiles, and (b) relating these subtypes to offense severity, the choice of a child victim, and recidivism.

Methods
We analyzed the juridical and medical files of 322 male JSOs aged 8.5 to 18.5 years (M = 14.14, SD = 1.94) living in Switzerland. Latent Class Analysis (LCA) was performed to derive subtypes based on 10 intra- and extra-familial ACEs. Associations between subtypes and offense characteristics as well as sexual and non-sexual recidivism were examined using logistic regressions.

Results
LCA identified five JSO-subtypes with (1) little/no ACEs (33.5%), (2) mainly neglect (18.6%), (3) mainly peer-related ACEs (21.7%), (4) mainly family-related ACEs (17.1%), and (5) multiple ACEs (9.0%). Subtypes were differently related to offense severity and the choice of a child victim. Sexual recidivism was only associated with the neglect-only subtype.

Discussion
JSOs display a heterogeneous group with distinct patterns of ACEs. A substantial number of JSOs have experienced family- and peer-related forms of abuse and neglect, which differently relate to offense characteristics and recidivism. Results indicate that a comprehensive assessment of ACE is needed both in research and therapy with JSOs to understand the development and maintenance of sexual offending.

3D)

Residual memory impairment in pure long-term MDMA users after controlling for polydrug use

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Introduction
Chronic MDMA use has repeatedly been associated with deficits in working memory (WM) and declarative long-term memory (DM). However, findings on MDMA effects specifically on WM are inconclusive yet, putatively because concomitant polydrug use has not been controlled for in most samples.

Methods
We compared the cognitive performance of 26 stimulant-free (pure) MDMA users, 25 stimulant-using polydrug MDMA users, and 56 MDMA-naïve controls by applying a comprehensive neuropsychological test battery. Current drug use was objectively determined by 6-month hair analyses.

Results
Cohen's d effect sizes for both comparisons 1) pure MDMA users vs. controls and 2) polydrug MDMA users vs. controls were highest for DM (d_{pure}=.90, d_{poly}=1.21), followed by WM (d_{pure}=.52, d_{poly}=.96), executive functions (d_{pure}=.46, d_{poly}=.86), and attention (d_{pure}=.23, d_{poly}=.70).

Discussion
Pure MDMA users showed strong DM impairments, while their WM deficits were less pronounced. In contrast, polydrug users displayed broad cognitive deficits in WM and executive functions in addition to DM deficits. The considerably large performance difference between pure and polydrug MDMA users may explain the inconsistencies in previous findings and underline the detrimental effect of stimulant use on WM. Consequently, pure long-term MDMA use is associated with decreased DM performance, while additional WM deficits in polydrug MDMA users are likely driven by stimulant co-use.

4D)

Frequencies and characteristics of self-reported hypomanic symptoms in adolescent psychiatric patients

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Introduction
Although screening tools for hypomanic symptoms in adults have been evaluated, data on the frequencies of hypomanic symptoms in adolescents are lacking. This is problematic, given that adolescence is the primary period when bipolar disorder symptomatology seems to emerge. We aimed to identify and characterize hypomanic symptoms in adolescent patients treated in the Department of Child and Adolescent Psychiatry Zurich, Switzerland.

Methods
The Hypomania Checklist (HCL-33) was developed to screen for lifetime hypomanic symptoms in depressed adults. In 2013-2014, 12-18 year-old patients completed the HCL-33 within a set of questionnaires as part of the diagnostic routine. Feasibility, psychometric properties and associations with current psychopathology were assessed.

Results
After exclusion of 12/285 (4.2%) due to >10% unanswered items, the sample comprised 273 patients, 15.0±1.5 year-old, 164 (60.1%) females, 184 (67.4%) outpatients, 57 (20.9%) inpatients, and 32 (11.7%) day-clinic patients. The HCL-total score was 14.7±5.6, which was not associated with age, sex, IQ, or treatment setting. A 2- or 3-factor solution represented the internal structure of the HCL-33. The first "active-elated" factor was similar in both solutions, whereas the second "irritable-risk taking" factor could be separated into "stimulation-seeking" and "irritable-distracted". Higher depressive and hyperactive symptoms were associated with higher HCL-total and "irritable-distracted" scores. Moreover, hyperactive symptoms correlated positively with the "stimulation-seeking" factor.

Discussion
Contrasting with state-independent HCL-scores in adult patients, current psychopathology affects HCL-scores in adolescent patients. Interestingly, severity of actual depression seems to be associated with increased HCL-total scores, especially with irritability as part of the "dark side" of hypomania.

5D)

Stimuli associated with food rewards influence goal-directed behavior in overweight, obese and normal-weight individuals

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Introduction
In our everyday lives, we are surrounded by cues (e.g. advertisements) reminding us of palatable food. It is believed that this "obsogenic" environment may lead to excessive food consumption and is therefore, contributing to the increasing prevalence of overweight and obesity. Previous research has shown that not all individuals are equally susceptible to these reward-predicting cues as potentially reflected by two different learning styles (i.e. goal- versus sign-tracking).

Methods
The aim of the present pilot study was to investigate the individual learning style my means of eye tracking using a Pavlovian-to-instrumental transfer (PIT) task in an overweight (ow), obese (ob) and normal-weight population (N normal-weight = 10, Now/ob = 17).

Results
Preliminary results showed that the food-related stimuli influenced goal-directed behavior significantly (PIT effect, $p < 0.05$). The BMI correlated negatively with this PIT effect ($r = -0.34$, $p < 0.05$) and learning style correlated with the total impulsivity score ($r = 0.349$, $p < 0.05$). More detailed analyses revealed a trend suggesting that that the largest PIT effect was found for overweight participants, particularly when they are goal-trackers.

Discussion
The trend in our data is in favor of the hyper- vs. hyposensitivity theory of reward in obesity predicting an inverted U-shaped relationship between BMI and reward sensitivity.

6D)

Functional impairment in posttraumatic stress disorder: a systematic review and meta-analysis

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Introduction
PTSD is a serious condition that is often associated with significant impairment in daily functioning. Empirically derived estimations for the magnitude of functional impairment in PTSD in distinct domains are essential e.g., for forensic evaluations in insurance medicine.

Method
A systematic literature search was conducted in medical databases. Random effects meta-analyses were conducted for the different functional areas according to the WHO International Classification of Functioning, Disability and Health (ICF) and standardized mean difference statistic (d) and their corresponding 95% confidence intervals were calculated.

Results
Forty-two studies were included in the meta-analysis. PTSD subjects, compared to healthy subjects, had higher impairment in the areas of general tasks and demands (d = 1.99, 95% CI [0.82, 3.14]), domestic life (d = 1.90, 95% CI [0.96, 2.84]), interpersonal interactions and relationships (d = 1.45, 95% CI [0.74, 2.16]), major life areas (d = 1.66, 95% CI [0.73, 2.60]), and community, social, and civic life (d = 1.70, 95% CI [1.01, 2.40]). PTSD subjects, compared to subjects with mental disorders other than PTSD, had higher impairment in self-care (d = 0.29, 95% CI [0.06, 0.52]), interpersonal interactions and relationships (d = 0.27, 95% CI [0.05, 0.49]), community, social, and civic life (d = 0.31, 95% CI [0.05, 0.57]). No differences between groups were found regarding impairment in mobility.

Discussion
Modest to large effect sizes were found for impairment in PTSD in many areas of daily functioning. These results suggest a significant impact of PTSD on public health and social insurance systems.

7D)

Understanding how acute posttraumatic stress relates to recovery from trauma: A network approach

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Introduction
Exposure to trauma is often followed by intense psychological suffering in the immediate aftermath of the event. While most individuals recover, a substantial minority develops severe chronic symptoms, such as a posttraumatic stress disorder (PTSD). Here we exploit recent network analysis approaches to investigate early PTSD symptoms as a complex dynamic system. Specifically, we aimed to (1) examine how the structure of acute posttraumatic stress relates to long-term recovery from PTSD and (2) identify symptoms and network indices as markers that can predict the development of chronic PTSD.

Method
We assessed acute posttraumatic stress and diagnosis of PTSD in assault survivors (n=205) presenting at an urban accident and emergency department within two weeks following the assault, as well as 6 months later, respectively. Using network analyses, we modeled acute posttraumatic stress and recovery, i.e., no PTSD, at 6 months post-trauma.

Results
Symptoms of acute stress were densely interconnected. Those who developed more chronic PTSD symptoms later reported more nightmares, heightened startle response, more cognitive avoidance, and a sense of foreshortened future early after trauma. Experiencing nightmares was, in turn, related to more intrusions and additional sleep problems and together, beside loss of interest, these three symptoms showed greatest interplay with other symptoms.

Discussion
Network analysis provides a novel perspective on psychopathological symptoms by considering reciprocal dynamics. Our results may help identify vulnerable individuals at an early stage and offer implications for prevention and intervention strategies, for instance by targeting interconnected symptoms using specific strategies, including sleep-related approaches.

8D)

Somatic Complaints During Childhood Predict Select Emotional Disorders During Young Adulthood in a U.S. Community Sample

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Introduction
Children with somatic complaints are at increased risk for emotional disorders during childhood. Whether this elevated risk extends into young adulthood—and to which specific disorders—has rarely been tested with long-term prospective-longitudinal community samples. Here we test whether frequent and recurring stomach aches, headaches, and muscle aches during childhood predict emotional disorders in adulthood after accounting for childhood psychiatric and physical health status and psychosocial adversity.

Method
The Great Smoky Mountains Study is a community-representative sample with 1,420 participants. Children/adolescents were assessed 4-7 times between ages 9 to 16. They were assessed again up to three times between ages 19 to 26. Childhood somatic complaints were coded when subjects or their parents reported frequent and recurrent headaches, stomach aches, or muscular/joint aches at some point when children were ages 9 to 16 years old. Psychiatric disorders were assessed with the Child and Adolescent Psychiatric Assessment and the Young Adult Psychiatric Assessment.

Results
Frequent and recurrent somatic complaints in childhood predicted adulthood emotional disorders. After controlling for potential confounders, predictions from childhood somatic complaints were specific to later depression and generalized anxiety disorder. Long-term predictions did not differ by sex. Somatic complaints that persisted across developmental periods were associated with the highest risk for young adult emotional distress disorders.

Discussion
Children from the community with frequent and recurrent physical distress are at substantially increased risk for emotional distress disorders during young adulthood. Preventions and interventions for somatic complaints could help alleviate this risk.

9D)

Emotion recognition, expressive suppression and dissociative symptoms in traumatized individuals with and without posttraumatic stress disorder

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Introduction
Previous research suggests that individuals with posttraumatic stress disorder (PTSD) may have difficulties recognizing facial emotional expressions. We aimed at replicating these findings. Moreover, we assessed if dissociative symptoms and suppression of one's facial expressions (expressive suppression, ES) affect the hypothesized emotion recognition (ER) deficits in PTSD.

Method
PTSD patients (n=34), traumatized (TC, n=34) and non-traumatized healthy controls (HC, n=29) were watching movies showing facial expressions and indicated which emotion was presented in each movie. ES during this task was assessed by self-report and by facial electromyography (EMG). Dissociative symptoms and potentially associated, autonomic changes occurring during the task were assessed by self-report and by changes in heart rate, respiratory sinus arrhythmia, and electrodermal activity

Results
Surprisingly, PTSD patients showed no ER deficits. Yet, post-hoc analyses revealed that for emotions presented with moderate intensity, higher numbers of traumatic events were linked to better recognition of negative (anger, fear, disgust, contempt) and poorer recognition of positive emotions (happiness, pride) across groups. Also, reaction times were longer in individuals with higher rates of childhood physical abuse and emotional neglect. Compared to TC and HC, PTSD patients reported more ES and showed diminished facial EMG responses to expressions of anger and joy, pointing to reduced facial reactivity. Self-report and EMG measures of ES were, however, unrelated to ER. Self-report but not psychophysiological measures of dissociative symptoms were linked to diminished ER abilities within the PTSD group.

Discussion
Emotion processing and ER may thus be related to (childhood) trauma, rather than to PTSD.

E)

Therapy Research: Drug Therapy, Psychotherapy, Healthcare Research

1E)

Clinical course of coercive measures among involuntary admitted psychiatric patients

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Introduction
The prevalence of coercion is still high in clinical routine and little evidence exists about its impact on clinical outcome. This study aims at characterizing a cohort of involuntarily admitted patients regarding sociodemographic and clinical variables.

Method
Descriptive analysis of patients' clinical data, the use of coercive measures (seclusion, restraint, involuntary medication) as well as other procedural aspects (intensive care, time until day-passes and revocation of involuntary admission, appeal to court) at the University Hospital of Psychiatry Zurich (expected N=1500).

Results
This is an ongoing project and the results presented are preliminary. To date datasets of about 400 patients are completed and statistical analysis of this group is presented. Coercive measures were used in 21%. Individuals with characteristics of "high utilizers" (male, violence, antipsychotic medication, ICD-10 F2-diagnosis) were more frequently subjected to coercion.

Discussion
Data prior to the revision of the Swiss civil code in 2013 revealed similar prevalence-rates but a higher rate of restraint. This may reflect the differences between clinics or a new trend in Switzerland. About half of the patients were hospitalized for the first time. The fact that coercion leads to avoidance of mental health care in some patients should be one of the reasons to urge its reduction, especially in the vulnerable group of first time hospitalizations.

2E)

Length of stay after involuntary admission related to the referring physician's psychiatric emergency experience

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Introduction
Although involuntary admission is a severe intervention in psychiatry that should always be regarded as an emergency measure, the knowledge about influencing factors is limited.
This study aimed at testing the hypothesis whether duration of involuntary hospitalisation and associated parameters differ for involuntary admissions mandated by physicians with or without routine experience with psychiatric emergency situations.

Method
We used a generalized linear model to analyze the length of involuntary hospitalisation and duration until day-passes were issued in 508 involuntarily admitted patients at the University Hospital of Psychiatry Zurich. The group of physicians with experience in psychiatric emergency situations included psychiatrists and emergency medicine physicians, while the non-experienced group consisted of physicians at somatic hospitals and general practitioners.

Results
Statistical analysis revealed significantly shorter durations of involuntary hospitalisation (one-sided log-rank test, $\chi^2=3.35$, $p<0.034$) and reduced time until day-passes were issued (one-sided log-rank test, $\chi^2=4.48$, $p<0.017$) for patients referred by non-experienced as compared to physicians with routine experience in psychiatric emergency situations. No covariate did contribute to this difference.

Discussion
Shorter length of stay following involuntary admissions by non-experienced physicians suggests that some involuntary admissions might be unnecessary and that alternatives such as out-patient crisis intervention, home-treatment, acute day clinic might have been sufficient. The implementation of specific training on how to conduct involuntary admission might decrease the rates of involuntary admissions. Also, limiting the authority to conduct involuntary admissions to physicians trained in psychiatric emergency situations could have a beneficial impact on reducing rates of involuntary hospitalisations.

3E)

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.

Method
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.

Outlook
Besides establishing ketamine in the treatment of therapy resistant depression, further research should focus on identifying clinical and electrophysiological phenotypes for presumably responding patients.

4E)

Efficacy of neurofeedback training in children and adolescents with ADHD as evaluated by systematic classroom observations and teacher ratings

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Introduction
In contrast to parent ratings, teacher ratings often fail to indicate significant improvement of ADHD symptoms after neurofeedback training (Sonuga-Barke et al., 2013). Teacher ratings, though, may be biased for several reasons. Systematic observations of classroom behavior may represent a blinded and ecologically valid alternative for measuring treatment outcome. However, their increased validity and sensitivity compared to teacher ratings for measuring change of ADHD symptoms have not been demonstrated yet and need further investigation.

Method
Children with ADHD (N=30) participated in a neurofeedback training of slow cortical potentials over 12 weeks. Prior to and post training, blinded raters conducted systematic observations of the subjects' on- and off-task behavior in the regular classroom. Using the same procedure, an untreated matched control group of unselected children (N=30) was observed twice at an interval of 12 weeks. Teacher ratings of ADHD symptoms were collected at both assessments.

Results
Analyses showed a significant time by group interaction on classroom off-task behavior. Ensuing within-group comparisons revealed significantly decreased off-task behavior in the treated children. The passive control group showed a significant increase in off-task behavior over time. Correlational analyses between changes in classroom behavior and changes according to teacher ratings resulted in small and non-significant associations.

Discussion
The data suggest improved classroom behavior of children with ADHD after neurofeedback training. These improvements were not correlated with teacher rated changes. However, more thorough analyses partly question the sensitivity of classroom observations to clinically relevant change given the unexpected change in untreated children.

5E)

Does HPA axis functioning predict treatment response in depressed patients? Findings from two systematic reviews and meta-analyses

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Introduction

Around 50% of depressed patients are not responsive to first-line treatments, such as antidepressants or psychotherapy. At the same time, a subgroup of patients is affected by hypothalamic-pituitary-adrenal (HPA) axis malfunctioning. As the HPA axis interacts with central monoaminergic systems and modulates cognitive processes, this subgroup may be less likely to profit from treatment. Our aim was to investigate whether HPA axis functioning predicts response to a) antidepressants and b) psychotherapy in depressed patients.

Method

The Cochrane Library, EMBASE, MEDLINE, and PsycINFO data bases were searched. Records were included in the systematic review if they looked at patients with depressive disorders receiving antidepressants or engaging in psychotherapy, with a pre-treatment HPA marker (e.g., cortisol) and post-treatment symptom measure (e.g., Hamilton). Summary statistics were extracted and aggregated for random-effects meta-analyses.

Results

In total, 73 studies were eligible. In terms of antidepressants, there was evidence from the systematic review that single nucleotide polymorphisms (SNPs) in genes related to corticotropin-releasing hormone, melanocortin, and pituitary adenylate cyclase-activating peptide predicted treatment response. The meta-analysis did not reveal any other HPA markers to be relevant (all $p > 0.168$). With regard to psychotherapy, both the systematic review and meta-analysis indicated that higher cortisol levels were linked with worse responses (mean ES = 0.42, $p = 0.012$).

Discussion

According to the here presented findings, a number of SNPs may predict response to antidepressants while cortisol seems to predict response to psychotherapy. Taken together, this implies that HPA markers could be used for indicative purposes in the treatment of depression.

6E)

Knowing and changing mental states: What can be learned from the self-appraisal of spontaneous arousal for neurofeedback performance ?

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Introduction
Over the past years neurofeedback (NF) has gained increasing popularity as a training method for children with ADHD in order to promote self-regulation of brain activity. However, little is known about the fundamental processes involved in NF. To our knowledge, it has not yet been examined if training success requires the awareness of aspects of one's own brain state that are modulated during a neurofeedback session. Therefore, we developed a self-appraisal task, where subjects are asked to report spontaneous arousal.

Method
Children with ADHD performed a self-appraisal task, which was conducted prior to typical NF training sessions of the slow cortical potentials. They were instructed to rate the level and change of spontaneous arousal in terms of direction (decrease, increase, or no change in arousal) and magnitude (large, small, or no change in arousal) during 8 secs intervals. Concomitantly, EEG activity was recorded.

Results
Preliminary results on performance in the self-appraisal task are reported with a focus on differences in individual patterns of learning across training sessions. Moreover, we will relate learning in the self-appraisal task to learning in NF.

Discussion
In this study, we examine how the ability to recongnize one's own inner states may be related to performance in NF training. Potential applications for NF training, as well as other forms of mental training, are discussed.

7E)

Mechanisms of treatment response of cognitve behaviour therapy in social anxiety disorder

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Introduction
Cognitive behaviour therapy (CBT) is an effective treatment of social anxiety disorder (SAD). Yet a number of patients respond not sufficiently to CBT. To the present, our understanding of the neurobiological basis of treatment response in SAD is limited and predicting outcome is difficult.

Method
26 outpatients with a current diagnosis of SAD underwent functional magnetic resonance imaging (fMRI) before and after a CBT group treatment (12 weeks). Subjects were presented with cued visual stimuli with prior known emotional valence (negative / neutral). Brain activity and functional connectivity of the right amygdala during pre-scan anticipation of negative stimuli were analysed as function of the treatment outcome (change in the Liebowitz social anxiety scale (LSAS)).

Results
Lower activation of the lateral prefrontal cortex (LPFC) and the superior temporal gyrus (STG) and higher activation in the right parahipocampal gyrus (PHG) during expectation of negative stimuli in the pre-treatment scan correlated with better treatment outcome. The strength of psychophysiological interaction (PPI) between the amygdala and the subgenual anterior cingulate (sgACC) / ventromedial prefrontal cortex (VMPFC) during expectation of negative stimuli in the pre-treatment scan was positively correlated with symptom reduction after the CBT program.

Conclusion
Activations and PPI with impact on the treatment-outcome as suggested by our study can be interpreted as correlates of lower avoidance and higher emotional reactivity in patients with better treatment outcome.

8E)

Mechanisms of change: An fMRI-study investigating changes in brain activity during a self-referential task after mindfulness based cognitive therapy in remitted depression

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Introduction
A growing body of literature supports the effectiveness of mindfulness based cognitive therapy (MBCT) for relapse prevention in remitted major depressive disorder (MDD).Specific neural mechanisms of these preventive effects are only partially understood. To further examine underlying changes in brain activity and identify potential targets for a neuro-feedback training, we examined remitted depressive patients before and after mbct using a self-referential task.

Method
Twenty-five remitted patients previously diagnosed with recurrent MDD were enrolled in a 10-12 week MBCT program. They underwent an fMRI scan before and after completing the program, respectively. During the scan, participants were asked to perform either a cognitive ("think") or a mindfulness based ("feel", instructed explicitly without mention of the word "mindfulness") self-reference task. Imaging was performed using Philips Achieva 3.0 T, fMRI data were statistically analyzed using Brain Voyager QX 2.4.8.

Results
Mindfulness increased from pre to post MBCT. Changes in brain activity from pre to post-MBCT were observed in the contrast between "feel" and "think" conditions. Increased brain activity differences were found in middle frontal gyrus, inferior parietal lobe, temporoparietal cortex, insular, caudate and precuneus regions. Decreased brain activity differences were found in inferior occipital and medial occipitotemporal cortex, prefrontal cortex, hippocampal and insular regions.

Discussion
MBCT training was associated with changes in brain activity in in brain regions involved in self-reference, attention and memory. Further analysis of the involved brain changes will contribute to better understanding the underlying processes and identifying brain correlates of the effect of MBCT on relapse prevention.