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DISSERTATION

Neurophysiological markers of psychiatric disorders: cerebrovascular reactivity as a state marker of depression and auditory sensory gating as a trait marker of schizophrenia

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1 Abstract

The mechanisms whereby emotions, cognitions, behaviours, or social factors are translated into physical disease; and conversely, how physical disease results in altered emotion, cognition, or behaviour cannot be answered without studying the brain. Until recently, psychiatric research relied predominantly on subjective assessment for diagnosis. Nonetheless, there is much promise for identifying and characterizing behavioural and biological markers intrinsic to complex psychiatric disorders in order to improve diagnostic standards, evaluation of disease outcome, treatment response and prevention. The disordered brain in common, severe and distinct psychiatric disorders, such as depression and schizophrenia, enables investigation of possible pathophysiological correlates. In the course of my work, this has been the overarching focus, albeit from various perspectives.

In the first study, the effect of depression on cerebrovascular reactivity (CVR), a prognostic factor for stroke risk, was evaluated in a group of acutely depressed individuals without vascular risk factors. In the second study, CVR was then measured on follow up after remission from depression. CVR was impaired during acute depression but improved after treatment, suggesting that the contribution to an increase stroke risk is a state rather than a trait marker. In the third study, we investigated the effects of schizophrenia and cannabis consumption on auditory P50 sensory gating, an indirect measure of pre-attentive inhibitory function of the central nervous system. The gating of the P50 component has previously shown deficits in schizophrenic patients, but data on co-morbid cannabis consumption are lacking. In otherwise healthy controls, chronic cannabis abuse impacts on sensory cortical circuits even after prolonged abstinence, while a P50 gating deficit was found in schizophrenia irrespective of cannabis consumption. Thus, our data point to differential effects of cannabis consumption in schizophrenic and in otherwise healthy controls. Moreover, our data corroborate the P50 gating as a potential trait marker of schizophrenia.

The different approaches used here explore physiologic parameters underlying brain activity in psychiatric disorders in order to find associations with possible co-morbid physiological dysfunctions and environmental factors; inversely, we also investigated how these physiologic dysfunctions may impact on brain activity.

Contents

2 Introduction

Pathophysiological markers are becoming increasingly valuable for the characterization of illness onset, severity and potential treatment response, as well as risks of co-morbidity. Although the search for neurophysiological anomalies, such as pre-attentive inhibition or blood flow here, hold promise for better understanding brain-body links, much work remains to be done to validate these measures. Here we studied the disordered brain in axis I mental disorders such as depression and schizophrenia by means of previously established physiological measures.

Depression has a lifetime prevalence of 17%, is the leading cause of disability as measured by 'years lived with disability' (YLDs) and by 'disability adjusted life years' (DALYs) and is the 2nd leading contributor to the global burden of disease today (WHO, 2011). In the last decade, depression has been linked to both cardiovascular and cerebrovascular disorders bi-directionally to the extent that depression is not only considered an independent risk factor of the metabolic syndromes but even an independent risk factor for ischemic heart disease (Joynt et al 2003). Research on depression and stroke initially focussed on the concept of "post-stroke depression" which views depression as a consequence of ischemic lesions. In the last decade, prospective epidemiological studies have suggested an association between stroke and depression, as depressed individuals have a higher prevalence of stroke even after adjusting for confounding factors (Salaycik et al 2007; Larson et al 2001). However, despite numerous studies having investigated the relationships of both cardiac and stroke morbidity and mortality with depression, the body of literature on stroke and depression is relatively limited, and the causal pathways linking depression to cerebrovascular disorders remain largely unknown. Cerebrovascular reactivity is a physiological measure that reflects the compensatory dilatory capacity of cerebral arterioles to a dilatory stimulus and plays a crucial role in maintaining a constant cerebral blood flow. A low CVR implies reduced blood flow and has been associated with increased risk of stroke. Identifying depression as a risk factor for cerebrovascular disease by investigating CVR in depressed subjects would have implications for preventing stroke morbidity and mortality. In addition, the extent to which the observed dysfunctions represent a state or a trait marker would offer further insight (Mayberg et al 1999): A trait marker represents the properties of the processes that have an antecedent, possibly causal role in the pathophysiology of a disorder; whereas a state marker reflects the status of clinical manifestation in patients (Chen et al 2006). Furthermore, the effects of antidepressant interventions on cerebrovascular-event risk reduction have not been sufficiently evaluated.

While in the case of depression, a state biomarker would be more insightful for treatment response and possibly, in this case, stroke prevention; schizophrenia offers the opportunity to investigate robust biological trait markers and the effects of potentially disease-exacerbating environmental factors on these. Schizophrenia has a lifetime prevalence of 1%, and despite improved treatment options one-third of the cases have a chronic course with high levels of individual impairment and socioeconomic cost. Apart from hallucinations and delusions, the disorder is marked by cognitive impairment and flattening of affect, also known as negative symptoms. The aetiology remains largely unknown, current theories point to an interaction of genetic susceptibility and environmental factors leading to clinical disease expression. Cannabis consumption is one of the environmental factors that is associated with psychosis in healthy individuals (Hall,

& Degenhardt 2008) and that worsens clinical outcome in subjects with other risk factors for psychosis (Cougnard et al 2007). Cannabis abuse has a high prevalence worldwide (Vega et al 2002; EMCDA, 2005). Disruption of brain function by chronic cannabis use has been shown in neuropsychological (Messinis et al 2006), electrophysiological (Struve et al 2003) and functional neuroimaging studies (Block et al 2002). The dysfunction of the endocannabinoid system allegedly plays a role in the inhibitory function for the brain (Szabo, & Schlicker 2005; Trettel, & Levine 2002). Scalp recordings of event-related brain potentials (ERPs) provide a powerful tool to investigate neural correlates of cortical gating mechanisms. Early dysfunction of neurophysiological measures of pre-attentive cognition may serve as an important nexus between future clinical symptoms and neurobiology. The auditory P50 sensory gating is an indirect electrophysiological measure of pre-attentive inhibitory function of the central nervous system in humans and thus a sensitive marker for neuronal alterations. Here we investigated whether it could serve as a discrete, measurable and easily manipulated intermediary neurobiological link between schizophrenia and disordered cognition, as has been suggested for depression (McNeely et al 2008). The P50 has previously shown deficits in schizophrenic patients (Adler et al 1982; Bramon et al 2004b) and their unaffected first-degree relatives (Siegel et al 1984) as well as in current otherwise healthy cannabis users (Patrick, & Struve 2000). Both alteration of this inhibitory function and cannabis abuse are hypothesized to precipitate schizophrenia onset, especially in subjects with other predisposing risk factors (Solowij, & Michie 2007). However, the long-term neurobiological consequences of cannabis abuse on cognition and in the development and course of schizophrenic disorders remain to be investigated.

3 Aims

The three studies summarised here evaluated the association of brain activity-related physiological measures with psychiatric disorders and possible co-morbidities. More concretely, for depression and stroke, we measured cerebrovascular reactivity (CVR) using duplex-ultrasound sonography. Specifically, we investigated the following questions: 1. Do we find a reduced CVR in acutely depressed patients? 2. Does CVR normalize after depression remission?

For schizophrenia with and without cannabis consumption, we measured the auditory P50 sensory gating. We aimed to answer the following question: Is the reduction of auditory P50 sensory gating in schizophrenia related to co-morbid cannabis consumption?

4 Research

4.1 Studies I and II

4.1.1 Background

The following two studies contribute to the same research agenda of investigating the effect of depression on cerebral blood flow by means of the pathophysiological marker of CVR.

We hypothesized (1) that CVR would be reduced in acutely depressed individuals compared to healthy controls and (2) that it would remain reduced despite remission of depression episode. In which case the observed dysfunction could be considered a trait marker and help to explain the increased stroke risk observed in depressed individuals. In the first study patients had acute depressive symptoms whereas in the second follow-up patients were euthymic.

4.1.2 Materials and methods

Subjects

In Study I, 25 right-handed individuals with acute depressive symptoms as defined by DSM-IV (as defined by structured clinical interview for DSM-IV, axis I disorder and Hamilton Depression Scale (HAMD)) (First et al 1995; Hamilton 1980), aged (48.48±14.40) without any cerebrovascular risk factors and 25 matched healthy control subjects underwent Doppler sonography exploration to determine CVR.

In Study II, 29 right-handed unipolar depressed patients defined as in study I, aged (42.15±12.93) without cerebrovascular risk factors (except for smoking) and 33 matched healthy control subjects had their CVR determined at two time points, defined by the acute phase (within 1 week of admission) and the remitted phase (mean of 21 months) of the patients' course of symptoms. Both smokers and non-smokers were evaluated. Smokers were asked to discontinue smoking for at least 60 minutes before the examination.

For both studies, prior to both measurement time points, patients and controls underwent a careful neurological and cardiologic examination, as well as ECG and blood chemistry tests. Clinical history was taken with particular attention to vascular risk factors. Any abnormalities in these examinations led to exclusion. Based on standard definitions, the presence of vascular risk factors was determined and led to exclusion, including cardiac arrhythmia, coronary heart disease, hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia.

Doppler protocol

Doppler sonography is a validated direct non-invasive method to measure blood flow velocity in the large brain arteries (Dahl et al 1992). We measured the cerebral blood flow velocity in both patients and controls using transcranial Doppler sonography. The increase of blood flow after stimulation with acetazolamide is a reliable and established method to calculate CVR (Dahl et al 1992). CVR is defined by the difference between maximal mean blood flow velocity at baseline, i.e. at rest, and maximal mean blood flow velocity after 2 minutes of acetazolamide stimulation.

CVR was determined using a TC 2-64 transcranial Doppler instrument. A 2-MHz transducer fitted on a headband and placed on the left temporal bone window was used to obtain continuous measurements of mean flow velocity (MFV) of the left middle cerebral artery. The highest signal was sought at a depth ranging from 45 to 55 mm. MFV was calculated in centimetres per second. Initially, baseline mean flow velocity (MFV) was obtained at rest by recording the continuous maximal MVF over 2 minutes during a 10-minute period. This was followed by a vasodilatory stimulation. Stimulation consisted of a 3-minute intravenous administration of 15 mg/kg body weight acetazolamide (ACZ). For 20 minutes following ACZ administration, MFV was recorded every second minute and maximal continuous increase in MFV over 2

minutes was noted. CVR was determined by calculating the difference between maximal mean flow velocity at baseline and the maximal mean flow velocity after stimulation. To exclude the presence of any intracranial stenosis that may interfere with the CVR measurement, a complete Doppler examination of anterior, middle and posterior arteries, of both internal and external carotid arteries and of the basilar and vertebral arteries was performed on all patients and controls.

Statistical analysis

In Study I, analysis of co-variance was used to assess the effect of diagnosis on maximal mean cerebral blood flow velocity after stimulation adjusting for age, gender and basal cerebral blood flow velocity. Model selection was based on F-tests using a stepwise selection approach. For all tests the significance level was set at alpha = 0.05, two-tailed.

In Study II, repeated measures analysis of variance (rmANOVA) was performed using a 2x2 design with the independent factors time-point and group to distinguish „between-factor group" and „within-group" variance. Again, maximal mean flow after stimulation as dependent variable, time-point (1st and 2nd measurement time-points) as within group factor and group (patients versus controls) as between group factor. Age and cigarette pack years were co-variates. Model selection was performed by Wilks' lambda for the within group comparisons and F-Tests for between group comparisons.

4.1.3 Results

Study I: Depressed patients showed a significantly reduced CVR compared to healthy controls (see table 1). As expected baseline blood flow had significant influence on maximal blood flow after stimulation, as did to a lesser extend age, but not sex.

Table 1

	patients (N=25)	controls (N=25)
Hamilton depression scale (mean/sd)	24.43/5.13	2.80/0.91
maximal mean flow velocity **baseline** (mean/sd)	50.64/11.16	52.80/12.70
maximal mean flow velocity after **stimulation** (mean/sd)	72.64/15.75	80.20/18.43

CVR = difference between maximal mean flow velocity at baseline and the maximal mean flow velocity after stimulation.

The covariance analysis yielded a significant main effect of diagnosis (T -2.620, $p<0.05$) and a significant effect for the covariates baseline blood flow (T 13.647, $p<0.00$) and age (T 2.140, $p<0.05$) but not for sex (T -1.212, $p>0.05$). CVR was measured during acute depressive episode in patients free of other traditional vascular risk factors (N=25) and in a healthy control group (N=25).

Study II: In line with Study I, CVR was significantly reduced in the acutely depressed patients as compared to the healthy control group. Contrary to our hypothesis, on follow-up i.e after remission, CVR of the patient group improved significantly and showed values comparable to those of the healthy controls.

Our final model included a group effect, a time effect and group-time interaction effects. We focussed particularly on patient and control group differences by evaluating the parameter estimates between them while adjusting for age and pack years. The parameter gives the difference between patients and controls. In

the rmANOVA a statistically significant main effect for time (F=6.81; p=0.012) and a significant time*group interaction were found (F=13.39; p=0.001) using multivariate testing. CVR was found to differ significantly in the patient group between baseline and follow up, but not in the healthy control group (see table 2). No significant influence of confounding variables (age, pack-years) was found in either group.

Table 2

parameter estimates							
dependent	group	B	SD	T	p-value	95% confidence interval	
						lower limit	upper limit
baseline	patients	20.958	1.673	12.530	.000	17.606	24.31
	controls	6.436	2.198	2.928	.005	2.030	10.841
follow-up	patients	27.292	1.744	15.65	.000	23.797	30.786
	controls	-0.958	2.292	-0.418	.677	-5.551	3.635

In sum:

1. CVR was significantly reduced in individuals with an acute depressive episode as compared to healthy controls, even after exclusion of vascular risk factors (Study Studies I and II).
2. On follow up, after depression remission, CVR of the patient group improved significantly and showed values comparable to those of the healthy controls (Study II).

4.1.4 Discussion

Our results in these two studies found that CVR in vascular risk-free depressed individuals was significantly reduced in comparison to healthy controls and in study II that CVR improved after successful treatment. This implies that CVR reflects a state rather than a trait marker. As a trait marker the contribution of depression to an increased stroke risk might only be true for a subgroup of patients, where CVR remains low, possibly in treatment resistant depression. It remains unknown after what time frame a reduced CVR leads to increased stroke risk. The pathophysiological mechanisms underlying this finding remain unclear and need to be further investigated. Nevertheless, to understand why CVR is reduced in depression, it is necessary to review the mechanisms that affect CVR and how they correlate with depression. Some hypotheses are discussed below:

1. Endothelial dysfunction, a key factor in the aetiology of atherosclerosis and thus a risk factor for reduced CVR, is impaired in patients with major depression (Broadley et al 2005) (Rajagopalan et al 2001). Similarly the production of nitric oxide, a vascular relaxing factor and inhibitor of proatherogenic processes, is decreased in the endothelium of depressed individuals (Chrapko et al 2006). Nitric oxide modulates the tone of the underlying vascular smooth muscle and inhibits several proatherogenic processes. A decreased production of NO adds to endothelial dysfunction. Although it has not yet been proven, endothelial dysfunction is thought to contribute to a reduced CVR.

2. Hyperhomocysteinemia induces hypertrophy of vascular muscle, which in turn leads to a reduction in maximum vasodilator capacity (Faraci, & Lentz 2004). Bottiglieri et al. (2000) among others have found elevated homocysteine levels in patients suffering from major depression. To date, no studies have investigated the link between hyperhomocysteinemia and CVR directly. High levels of homocystein in depressed patients may be explained by poor diets or a higher rate of polymorphism of enzymes essential for the homocysteine metabolism (Bjelland et al 2003).

3. A further characteristic feature of depression is the abnormal function of the hypothalamic-pituitary-adrenal (HPA) axis – which may lead to cortisol hypersecretion and failure of normal suppression of cortisol after oral dexamethasone. Chronic cortisol elevation is associated with the onset of early atherosclerosis. Cortisol accelerates endothelial dysfunction and induces a down-regulation in plasma NO-levels (Broadley et al 2005).

4. Animal studies have found that neuroadrenergic stimulation results in vasoconstriction in cerebral resistance vessels (Szabo et al 1983; Kogure et al 1979). While enhanced cerebral blood flow induced by parasympathetic activity could be normalized by activation of sympathetic nerves, the reverse phenomenon – i.e., parasympathetic normalization of the sympathetically induced cerebral blood flow reduction – did not occur (Morita-Tsuzuki et al 1993). Hence in a situation of sympathetic hyperactivity, auto-regulation of cerebral blood flow might be reduced in an elevated cerebrovascular tone. Indeed there are reports of parasympathetic/sympathetic inbalance in depressive patients (Tulen et al 1996; Guinjoan et al 1995). This could also underlie the observed reduction in CVR.

A limitation of these two studies is that almost all the patients were treated with one or more antidepressants and that the degree to which psychoactive drugs affect CVR remains largely unknown. Thus medication is a possible factor of influence that cannot be entirely controlled for. A further limitation is the heterogeneity of the studies, as the second study included smokers and non-smokers.

The extent to which CVR or sub-clinical lack of reactivity might be classified as early sub-clinical disease; serve as a pathophysiological measure to identify treatment response, sub-clinical stroke risk or subgroups of depression; as well as a means for identification of depression or stroke risk in family studies, will require studies with larger study size.

4.2 Study III

4.2.1 Background

Here we postulated that cannabis use (1) deteriorates sensory gating and (2) that this effect is more pronounced in schizophrenic patients as compared to otherwise healthy controls. We investigated P50 sensory gating in long-term abstinent (more than 28 days) schizophrenic and healthy control cannabis users and compared these to non-drug using schizophrenic patients and healthy controls.

4.2.2 Materials and methods

Subjects We included 4 groups: (i) schizophrenic patients without cannabis consumption (SZ); (ii) with high-frequent cannabis consumption before the onset of schizophrenia, currently abstinent for at least 28 days (SZCA); (iii) healthy controls without any significant drug abuse (CO) and (iv) controls with chronic cannabis abuse (otherwise healthy), currently abstinent for at least 28 days (COCA). All subjects had no significant use of other drugs. The patient and control groups were comparable in their demographic details. The schizophrenic patients were stable in- and outpatients, diagnosed according to DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994) by the consensus of two independent experienced clinical psychiatrists. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS, Kay et al 1987). All, but one patient, were treated with atypical antipsychotic medication. Cannabis abuse was only allowed up to 28 days before the date of the individual testing in both cannabis-abusing groups (SZCA, COCA) and otherwise led to exclusion. A urine drug-screening test was performed at the time of investigation. The drug abuse data was obtained through medical records, self-report and medical history by proxy. Data included: age at first consumption and age at onset of regular daily use, average daily dose and number of years of regular cannabis abuse.

Auditory P50 measurement, data processing and gating ratio Evoked responses were recorded with a tin electrode on Cz according to the international 10/20 system referred to both earlobes. An electrode on the forehead served as ground. Eye movements were recorded across an electrode placed 1 cm lateral to the left eye. Electrode impedance was less than 10 kΩ. Data were collected with a sampling rate of 500 Hz and an analogous band pass filter (0.15-100 Hz). Auditory stimuli were 100 identical pairs of clicks (duration: 1 ms, 90 dB) separated by 500 ms with one pair presented every 8-10 s in a pseudo-randomized manner through earphones. Before recording, all subjects underwent a simple hearing threshold test. After segmentation (350 ms pre-stimulus and 800 ms post-stimulus) and exclusion of segments showing activity greater or lower than 80 mV, the data was digitally filtered and baseline-corrected. For each subject the remaining sweeps were averaged. Latencies and amplitudes of the P30, N40 and P50 were analyzed based on an automatic peak-detection (Brain vision analyzer Version 1.1, Munich, Germany) in combination with a visual control (blind to the groups).

The P50 component was defined as a positive response between 40–80 ms post-stimulus, preceded by a P30 wave in a 20–50 ms range. If there was no identifiable P30, the most prominent positive component in the P50 time range was used as P50. The N40 was defined as the most prominent negative peak between P30 and P50. If this was equivocal, the most negative peak preceding the P50 was used as N40. The P50 amplitude was measured as N40-peak to P50-peak difference. If no P50 amplitude was identifiable for the first stimulus (P50-1), the subject was excluded, and if that was the case for the second stimulus (P50-2), the P50 amplitude was set at zero and interpreted as maximal suppression in accordance with Dolu et al. (2001). The P50 gating was calculated as the ratio (%) of the P50 amplitude of the second stimulus to the P50 amplitude of the first stimulus: amplitude P50-2° / amplitude P50- 1° * 100.

Statistical analysis We used non-parametric testing for group comparison of the P50 gating and the demographic and clinical parameters because of the small sample size. Kruskal–Wallis test and Chi^2 test were used for comparison of more than two groups, Mann–Whitney test and Chi^2 test for comparison of two groups. Post-hoc tests of P50 gating were done with the Mann–Whitney test. The significance levels were Bonferroni–Holm corrected. The correlation analyses between P50 gating and average daily cannabis dose and number of daily consumption years were done with a zero-order correlation. The latter was further corrected with a partial correlation controlling for age. Data were checked for normality prior to correlation analysis using Kolmogorov–Smirnov statistics. All tests were two-tailed. The significance level was set as $p<0.05$, a statistical trend was assumed for $p<0.1$.

4.2.3 Results

P50 gating, however, did show significant difference between the groups ($p=0.02$; Kruskal–Wallis test). This was due to a significant P50 gating difference between otherwise healthy cannabis controls (COCA) and the other three groups (CO: $p=0.027$; SZ: $p=0.024$; SZCA: $p=0.046$) as shown by the post-hoc pairwise t-test. No further post-hoc pairwise testing was done for the other groups because the mean and standard deviation were similar. No significant differences in latency and amplitude of the P50 were found between the four groups.

We also compared P50 gating between the pooled schizophrenic patients (SZ and SZCA: 42.7±19.2) and the healthy controls (CO: 37.4±17.9) – P50 gating did not differ significantly between the pooled groups (MWU=206.0, Z=−0.86, p=0.39).

We used the Pearson coefficient to evaluate correlations between P50 gating, number of daily consumption years and average daily dose: In the cannabis control group (COCA) the Pearson coefficient showed a positive correlation between P50 gating, number of daily consumption years (r=0.81; p=0.003) and average daily dose (only a statistical trend (r=0.55; p=0.079)). The correlation between P50 gating and number of daily consumption years remained significant after correction for age of the subjects (rage=0.69;p=0.026), but age and P50 gating were not significant after correcting for number of years with daily consumption (ryears=0.35; p=0.3). No significant correlation was found between gating and age of first consumption (r=0.25; p>0.1) and age of daily regular cannabis consumption (r=0.54, p>0.1). In the schizophrenic patients with cannabis abuse, no cannabis-related parameters showed significant correlation with respect to gating (number of years with daily consumption: r=0.01, the average daily dose: r=0.19, age at the beginning of first consumption: r=−0.25 and regular consumption: r=−0.08; for all parameters p>0.1).

4.2.4 Discussion

The main finding of the study was a P50 sensory gating deficit in otherwise healthy cannabis-abusing controls when compared to both schizophrenic patients with and without chronic cannabis abuse. In contrast, schizophrenics with cannabis abuse showed no significant differences in P50 sensory gating compared to schizophrenics without cannabis use or to non-cannabis abusing healthy controls. The mean gating ratio was slightly higher in schizophrenic patients with cannabis use than in those without cannabis use and non-cannabis-using healthy controls, but this was not statistically significant. Thus, as hypothesized, cannabis has a differential effect in schizophrenic patients and otherwise healthy controls with respect to sensory gating. However, the hypothesized differences in P50 sensory gating in schizophrenic patients with and without cannabis abuse were not confirmed.

Here are some of the possible explanations for the lack of differences in P50 sensory gating between the schizophrenic groups:

1. Previous studies have suggested that drug use pre-onset of psychotic symptoms might not affect P50 sensory gating as post-onset use does (Boutros et al 2004). We only included schizophrenic patients with pre-onset cannabis use. One could speculate that it is the cumulative effect of the drug, in this case cannabis, on an already biochemically sensitive brain that affects P50 sensory gating.

2. Evidence in non-drug using schizophrenic patients suggests that atypical antipsychotics can 'renormalize' P50 gating (Becker et al 2004; Light et al 2000).

3. A number of studies found no significant deficit in sensory gating by p50 ratio in schizophrenic patients as compared to controls. Our study might not have been sensitive enough to detect a P50 sensory gating deficit; however, having found gating deficits in the control groups, this is unlikely. Botrous (1993) found differences between subtypes of schizophrenia, paranoid subtype having normal P50 gating as compared to non-paranoid/disorganised. In patients groups the paranoid subtype predominated, this might have biased the results.

4. Important however is the reduced P50 gating found in frequent but otherwise healthy cannabis users. This indicates a disruption of neuronal information processing in a manner typically observed in unmedicated schizophrenic patients (Bramon et al 2004a). This could be due to a) otherwise healthy

frequent cannabis users inherently having a disrupted P50 gating prior to drug use onset or b) high-frequent cannabis abuse leading to an alteration of neuronal substrates underlying sensory gating as typically observed in schizophrenia. Addressing such a research question will be the focus of future studies.

A study by Solowij (1995) found an impaired ability to filter out irrelevant information on an attentional level. This impairment was positively correlated to the cumulative drug exposure duration in short (24h) and long-term (42days) abstinence of cannabis abusing subjects. This corroborates our results showing an impaired preattentive filter of irrelevant information, progressing with the cumulative duration of exposure to cannabis in long-term abstinent users. Thus, cannabis abuse can disrupt preattentive and also selective attentive information processing and sensory gating even after long-term abstinence. The physiological mechanism underlying P50 sensory gating impairment in chronic cannabis users remains unclear. The endocannabinoid system may be involved in rapid modulation of synaptic transmission in the CNS (Fonseca et al 2001). Endocannabinoids would be predicted to selectively suppress gamma oscillations (Wilson, & Nicoll 2002), which underlie in part the P50 potential and gating (Clementz et al 1997). The hypothesis that frequent cannabis abuse leads to an alteration of neuronal substrates underlying sensory gating (as that typically observed in schizophrenia) is central to research on the effects of cannabis as an environmental factor influencing mental health, and more specifically schizophrenia. This is especially relevant considering the prevalence of cannabis use worldwide and especially by schizophrenic patients (Barnes et al 2006). There is evidence suggesting an involvement of the cerebral endocannabinoid system in the pathology of schizophrenia (for review see Ujike, & Morita 2004), cannabis abuse in these patients may thus impair the function of this system even further.

To conclude, our data provide some evidence of cannabinoid-induced modulation of sensory gating and indicate that chronic cannabis abuse may affect sensory cortical circuits even after prolonged abstinence, at least in otherwise healthy cannabis users. The data also point to a possible differential effect of cannabis in otherwise healthy chronic and in schizophrenic users. Future studies with larger samples and including additional drugs are needed to corroborate the specificity of these results.

5 Conclusions and future directions

These three studies explored the use of pathophysiological indices in psychiatric disorders as an additional marker to evaluate co-morbidity risks, treatment and disease outcome. The many factors influencing the outcome of psychiatric diseases make it challenging to find individual pathophysiologic disease markers. However, identifying objective measures that have diagnostic potential, and identifying them as state or trait markers, will help to advance diagnostic classification, clinical research and future treatment options.

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Erklärung zur Vorlage im Promotionsbüro der Charité über den Anteil von Frau Gómez-Carrillo de Castro an den folgenden drei Publikationen

[1] Rentzsch J, Penzhorn A, Kernbichler K, Plöckl D, **Gómez-Carrillo de Castro A**, Gallinat J, Jockers-Scherübl MC.Differential impact of heavy cannabis use on sensory gating in schizophrenic patients and otherwise healthy controls. Exp Neurol. 2007 May;205(1):241-9.

[2] **Gómez-Carrillo de Castro A**, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P. Cerebrovascular reactivity in depressed patients without vascular risk factors. Journal of Psychiatric Research 2008;42(1):78-82.

[3] Lemke H, **Gómez-Carrillo de Castro A**, Schlattmann P, Heuser I, Neu P. Cerebrovascular reactivity over time course - from major depressive episode to remission. Journal of Psychiatric Research Feb 2010, Volume 44, Issue 3:132-136.

Hiermit bestätigen die Unterzeichnenden, dass Frau Gomez-Carrillo de Castro folgende Anteile an den drei Publikationen erbracht hat:

1 50% an Entwurf und Anfertigung der Publikation in der vorliegenden Form.

2 75% Beitrag im Einzelnen: Durchführung aller Doppleruntersuchungen unter Anleitung, Screening und Rekrutierung der Patienten und Probanden, Literaturrecherche, Verfassen des Artikels.

3 25% Beitrag im Einzelnen: Mitarbeit bei Untersuchung, Screening und Rekrutierung der Probanden/Patienten, Literaturrecherche, Mitarbeit bei Verfassen des Artikels.

PD Dr. med. Peter Neu
(Doktorvater)

Ana Gomez-Carrillo de Castro
(Doktorandin)

8 Selected Publications

8.1 Cerebrovascular reactivity in depressed patients without vascular risk factors.

Cerebrovascular reactivity in depressed patients without vascular risk factors.
A Gómez-Carrillo de Castro, M Bajbouj, P Schlattmann, H Lemke, I Heuser, P Neu (2008)
Journal of psychiatric research 42 (1) p. 78-82

8.2 Cerebrovascular reactivity over time-course-From major depressive episode to remission.

Cerebrovascular reactivity over time-course-From major depressive episode to remission.
H. Lemke, A.G.C. Castro, P. Schlattmann, I. Heuser, P. Neu (2010) Journal of psychiatric research 44 (3) p. 132–136

8.3 Differential impact of heavy cannabis use on sensory gating in schizophrenic patients and otherwise healthy controls.

Differential impact of heavy cannabis use on sensory gating in schizophrenic patients and otherwise healthy controls. J. Rentzsch, A. Penzhorn, K. Kernbichler, D. Plöckl, A. Gómez-Carrillo de Castro, J. Gallinat, M.C. Jockers-Scherübl (2007) Experimental neurology 205 (1) p. 241–249

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen
in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Complete publication list

Papers

Emotion modulates the effects of endogenous attention on retinotopic visual processing. Gomez A, Rothkirch M, Kaul C, Weygandt M, Haynes J-D, Rees G, Sterzer P. (accepted in Neuroimage))

Cognitive impairment and cerebral atrophy associated with IgA antibodies to NMDA receptors. Prüss H, Höltje M, Maier N, Gomez A, Buchert R, Harms L, Ahnert-Hilger G, Schmitz D, Terborg C, Köller H, Kopp U, Klingbeil C, Borowski K, Kohler S, Schwab JM, Stoecker W, Dalmau J, Wandinger KP. (Submitted)

Cerebrovascular reactivity over time-course-From major depressive episode to remission. H. Lemke, A.G.C. Castro, P. Schlattmann, I. Heuser, P. Neu (2010) *Journal of psychiatric research* 44 (3) p. 132–136

Towards an evolutionary framework of suicidal behavior. Hilario Blasco-Fontecilla, Jorge Lopez-Castroman, Ana Gomez-Carrillo, Enrique Baca-Garcia (2009) *Medical hypotheses* 73 (6) p. 1078-9

Cerebrovascular reactivity in depressed patients without vascular risk factors. A Gómez-Carrillo de Castro, M Bajbouj, P Schlattmann, H Lemke, I Heuser, P Neu (2008) *Journal of psychiatric research* 42 (1) p. 78-82

Comparison of midlatency auditory sensory gating at short and long interstimulus intervals. Johannes Rentzsch, Ana Gomez-Carrillo de Castro, Andres Neuhaus, Maria C Jockers-Scherübl, Jürgen Gallinat (2008) *Neuropsychobiology* 58 (1) p. 11-8

Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. M.C. Jockers-Scherübl, T. Wolf, N. Radzei, P. Schlattmann, J. Rentzsch, A. Gómez-Carrillo de Castro, K.P. Kühl (2007) *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 31 (5) p. 1054–1063

Differential impact of heavy cannabis use on sensory gating in schizophrenic patients and otherwise healthy controls. J. Rentzsch, A. Penzhorn, K. Kernbichler, D. Plöckl, A. Gómez-Carrillo de Castro, J. Gallinat, M.C. Jockers-Scherübl (2007) *Experimental neurology* 205 (1) p. 241–249

Posters

Conference Depression: Brain Causes,Body Consequences at Institute of Psychiatry
'Cerebrovascular reactivity in depressed patients w/o vascular risk factors' *April 2006*

Human Brain Mapping Conference 2010
'Emotional information modulates the effects of attention on retinotopic visual processing', June 2010

Independence declaration

Ich, Ana Gómez-Carrillo Castro, erkläre, dass ich die vorgelegte Dissertation mit dem Thema

"Neurophysiological markers of psychiatric disorders: cerebrovascular reactivity as a state marker of depression and auditory sensory gating as a trait marker of schizophrenia"

selbst und ohne die unzulässige Hilfe Dritter verfasst, keine anderen als die angegebenen Quellen und Hilfsmittel benutzt und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Berlin, den 24. Februar 2011 Ana Gómez-Carrillo Castro

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