Aus der Klinik für Psychiatrie und Psychotherapie
der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

DISSERTATION

“The brain and its intrinsic functional architecture – Investigations using resting-state functional magnetic resonance imaging“

zur Erlangung des akademischen Grades
Doctor rerum medicinalium (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 10.03.2017

Content

Abstract

English - The human brain is a network of interconnected regions, both on an anatomical and functional level. Although the brain´s intrinsic functional architecture provides a crucial basis for our behavior, it is still incompletely characterized. Using a multi-methodological approach across three studies, the work presented in this thesis aimed to explore and characterize different aspects of the brain´s intrinsic functional architecture, as measured with resting-state functional magnetic resonance imaging (rs-fMRI). Specifically, study 1 investigated the relationship between amygdala resting-state functional connectivity (rs-FC) within the face processing circuit and the personality dimension of neuroticism, as well as how the 5-HTTLPR/rs25531 polymorphism impacts this relationship. Here, we provide first evidence that variants of the 5-HTTLPR/rs25531 genotype and different levels of neuroticism may be linked to rs-FC between amygdala and occipital face area, which, in turn, may partly account for altered processing of negative facial emotions. In the second study we explored the potential benefits of global signal regression (GSR) as a crucial preprocessing step in rs-fMRI analyses for unmasking 'true' inter-regional relationships in brain networks. Here we provide initial evidence for the potential of amygdala rs-FC to segregate face-sensitive areas within the fusiform gyrus when GSR is applied. This illustrates how GSR might be used in rs-fMRI data analysis as a method to segregate functionally distinct brain areas. Study 3 describes the development of "GraphVar", a user-friendly toolbox for comprehensive large-scale graph theoretical analyses of brain networks, which facilitates future research on complex brain networks and their topology. This toolbox will make graph theoretical analysis methods readily available to a broad audience of brain researchers, and has already been downloaded over 2000 times since its first release.

German - Das menschliche Gehirn besteht aus einem Netzwerk anatomisch und funktionell verknüpfter Regionen. Obwohl die funktionelle Architektur dieses Netzwerkes maßgebend unser Verhalten beeinflusst, ist sie noch zu großen Teilen unerforscht. Mit Hilfe funktioneller Magnetresonanztomographie und Messungen des Gehirns im Ruhezustand (rs-fMRI) versucht die vorliegende Arbeit durch multimethodale Ansätze in drei Studien zur weiteren Charakterisierung seiner funktionellen Architektur beizutragen. Studie 1 untersuchte zu diesem Zweck den Zusammenhang zwischen funktionellen Verbindungen der Amygdala im Gesichtserkennungsnetzwerk und der Persönlichkeitsdimension Neurotizismus sowie des assoziierten Polymorphismus 5-HTTLPR/rs25531. Die Studie zeigte, dass die Stärke der Verbindung von Amygdala zum okzipitalen Gesichtsfeld mit Ausprägungen des 5-HTTLPR/rs25531 Genotyps und zugleich auch mit Ausprägung der Persönlichkeitsdimension Neurotizismus variiert. Die Ergebnisse legen nahe, dass die Variation dieser Verbindungsstärke grundlegend für interindividuelle Unterschiede in der Verarbeitung von negativen Gesichtsausdrücken sein könnte. Studie 2 untersuchte die Möglichkeit, durch Herausfiltern des im Ruhezustand vorhandenen globalen Signals spontaner neuronaler Fluktuationen aus den rs-fMRI Daten (GSR) die im Gehirn verankerten „echten“ Netzwerkverbindungen regional zu spezifizieren. Die gewonnenen Ergebnisse zeigen, dass die funktionellen Verbindungen der Amygdala im Gesichtserkennungsnetzwerk durch das Herausfiltern dieses Signals direkt den Gesichtserkennungsregionen im Gyrus Fusiformis zugeordnet werden können. Diese Resultate deuten darauf hin, dass GSR in rs-fMRI Daten auch in anderen Teilen des Gehirns genutzt werden könnte, um Regionen unterschiedlicher Funktionalität voneinander abzugrenzen. Studie 3 diente der Entwicklung von „GraphVar“, einem benutzerfreundlichen Computerprogramm zur umfassenden Analyse von Gehirnnetzwerken und deren Topologie. Dieses Programm wurde mit der Hoffnung entwickelt, verschiedene Netzwerkanalysemethoden und deren Anwendung für eine große Zahl von Hirnforschern zugänglicher zu gestalten, und zählt seit seiner Veröffentlichung bereits über 2000 Downloads.

Introduction

Resting-state fMRI and the brain´s intrinsic architecture

During the past decade, advances in functional magnetic resonance imaging (fMRI) driven neuroscience have led to the notion that the human brain is a network of functionally interconnected regions that share information continuously. A methodological development with major contribution to this understanding is resting-state fMRI (rs-fMRI), with which functional connectivity between brain regions can be inferred by temporal co-variation of spontaneous fluctuations of the fMRI blood oxygen level dependent (BOLD) signal during rest[1,2,3,4]. Resting-state functional connectivity (rs-FC), in turn, is hypothesized to reflect the brain´s intrinsic functional architecture, thereby providing the functional fundament for task-related brain processes, which can then be associated with behavior, and, for example, personality[5,6,7,8,9]. A variety of techniques exists to characterize the functional connectivity, including (among others) well-established approaches focusing on connections of specific brain regions (seed-based analyses), or relatively newer methods that examine and characterize the overall structure of brain networks with graph analysis routines[1,2,3,4]. Although these methods have revealed a wealth of new insights into the connectivity of the brain in both health and disease[10,11,12,13], a thorough understanding of the brain´s connectome that can account for its massive number of interacting components and associations to individual behavior still remains an ongoing endeavor.

As outlined in the following, the work presented in this thesis contributes to this journey by further characterizing and exploring different aspects of resting-state functional connectivity, offering a multi-methodological approach across three studies. Specifically, by using seed-based rs-fMRI analyses, we studied the relationship between the intrinsic functional architecture of the face processing circuit and the personality dimension of neuroticism, as well as how an associated genetic polymorphism may impact this relationship (study 1)[14]. Second, we explored the potential benefits of the recently much-debated preprocessing step of global signal regression in rs-fMRI analyses for unmasking 'true' inter-regional relationships within brain networks (study 2)[15]. Third, we developed a user-friendly toolbox for comprehensive large-scale graph theoretical analyses of brain networks to facilitate future research on complex brain networks and their topology (study 3)[16].

The brain´s intrinsic architecture I – *Association of neuroticism and 5-HTTLPR/rs25531 to amygdala resting-state functional connectivity in the face processing circuit*

Personality is an established research area but little is known about the neural correlates. Personality can be described as trans-situational consistent and is thought to be strongly genetically influenced[17,18]. A suitable methodological approach to investigate the relationship between personality and brain function is rs-fMRI as it offers the possibility to characterize inter-individual differences in intrinsic brain activity while avoiding the constraints of task-based approaches (i.e., situational dependence). Here, we focus on the personality dimension of neuroticism and its presumed association with variants of the 5-HTTLPR polymorphism to the intrinsic functional architecture of the face processing circuit as outlined in the following. Neuroticism is associated with experiences of negative affect as well as anxiety and mood disorders, and can be considered among the best predictors for depression[19,20,21,22]. A previously described emotion processing bias in neuroticism[23] and depression[24,25] relates to altered perception of negative facial expressions. On a neural basis, individuals high in neuroticism (i.e., anxiety prone subjects) and subjects with depression showed elevated amygdala activity in response to negative facial expressions[26,27,28].

Neural activity of the amygdala is modulated by the serotonin transporter polymorphism (5-HTTLPR)[29], which entails a short (s) and a long (l) variant[30,31,32] and was shown to be functionally triallelic due to an A to G substitution within the l-allele caused by the single nucleotide polymorphism (SNP) rs25531 (s, l_A, and l_G alleles, low-expressing: s and l_G, high-expressing: l_A)[33]. The s-allele is associated with greater amygdala activity in response to negative stimuli[34,35,36], and altered resting state activity of the amygdala[37,38]. Although previous studies were not consistent in replication (e.g., negative association studies[39,40,41]), some studies provided evidence for an association of the 5-HTTLPR s-allele with traits related to neuroticism and anxiety, hypothesized to be modulated by serotonin[42,43,44,45], as well as with psychiatric disorders, particularly affective disorders[46,47,48,49,50,51]. Similar to altered amygdala response during face-emotion processing in anxiety prone subjects, some studies observed differences in amygdala activity in response to emotional faces when comparing subjects taking selective 5-HT reuptake inhibitors with subjects taking placebos[52,53,54,55]. This points towards a pivotal role of 5-HT in emotional expression processing within the amygdala.

A region crucial for face perception is the fusiform gyrus (FFG)[56,57,58]. FFG activity is modulated by inputs from the amygdala[59,60,61], which was further substantiated by recent task-based fMRI findings that showed that the amygdala exhibits functional connectivity to the FFG,

thereby influencing FFG function during face perception[62]. In addition to previous findings of neuroticism and 5-HTTLPR influence on amygdala activity, research showed that neuroticism[28] and 5-HTTLPR[34,63] also impacted FFG activity in response to emotional facial expressions. Thus, as suggested by the reviewed literature, it seems that this critical connection between the amygdala and the FFG, critical for processing emotional facial expressions, may depend on levels of 5-HT neurotransmission, and may therefore vary with different levels of anxiety related traits such as neuroticism.

The brain´s intrinsic architecture II – *Effects of global signal regression in revealing 'true' inter-regional relationships within brain networks*

To map the brain´s intrinsic functional architecture, a common data preprocessing step in rs-fMRI analyses is the removal of spontaneous BOLD fluctuations common to the whole brain – the so called global signal regression (GSR). Originally introduced with the purpose of enhancing signal-to-noise through reduction of non-neural noise, its usefulness has recently become a topic of ongoing discussions[64]. As regression against the global mean signal has been shown to shift correlation distributions towards a mean correlation value close to zero, a fundamental argument against application of GSR is the artificial introduction of negative correlations[65,66]. On the other hand, and in favor of GSR, it has been argued that GSR may also remove a true shared covariation in firing rate (i.e., a true global neuronal signal), thereby revealing relationships of neuronal populations otherwise masked by the dominant global signal[67,68,69]. Here, we offer support for another potential benefit of GSR, based on an observation that was done within the context of data analyses in study 1 of this thesis[14]. During data analyses it was observed that, when GSR was performed, amygdala rs-FC delineated subregions of the FFG that spatially correspond to the commonly reported face sensitive areas, namely the occipital face area (OFA) and fusiform face area (FFA). Specifically, we observed that after applying GSR a cluster of *positive* amygdala rs-FC approximately corresponded to the FFA, while a cluster of *negative* rs-FC corresponded best to the OFA, whereas not applying GSR resulted in one homogeneous positive cluster comprising both the OFA and FFA. In the current study we describe this observation in detail, test for reliability of effects over different samples, and examine whether these amygdala rs-FC defined clusters may indeed correspond to the face sensitive areas in the FFG.

The brain´s intrinsic architecture III – *Graph-theoretical analysis of brain connectivity and the unmet need for accessible software*

The overall structure of brain networks and its connectivity of the brain can be described by defining brain networks, which comprise regions of interests ("nodes") and interregional structural or functional connections ("edges"). Graph theory, the mathematical study of networks, provides a powerful and comprehensive formalism of global and local topological network properties of complex structural or functional brain connectivity[2,3]. Application of graph theoretical measures to clinical populations has revealed differences in these properties in Alzheimer's disease[70], attention-deficit hyperactivity disorder[71], multiple sclerosis[72], schizophrenia[73,74], pathological gambling[75], heroin dependence[76], and many other neurological and psychiatric disorders. Apart from describing topological network properties, graph theory also provides a framework for identification of anatomically localized sub-networks associated with particular effects of interest (such as candidate genotype group differences or correlations with neuropsychological test scores) across the entire brain[77]. Although recently developed software packages such as the Brain Connectivity Toolbox[3] have contributed to graph theory's increasing popularity for characterization of functional brain networks, most comparably comprehensive software packages are command-line based and require programming experience. This may lead to time-consuming, complicated, and error prone operations for researchers without sufficient computational background, and place such analyses out of reach for scientists whose research would otherwise benefit from graph-theoretical analyses. The development of accessible software for such analyses represents an important and unmet need. Here we addressed this need by developing "GraphVar", a user-friendly graphical-user-interface (GUI)-based toolbox for comprehensive graph-theoretical analyses of brain connectivity.

Hypotheses

Study 1: The aim of this current study was twofold: first, we specifically focused on the association of 5-HTTLPR/rs25531 and neuroticism to rs-FC between amygdala and FFG. Here, we hypothesized that different levels of 5-HT neurotransmission (as defined by 5-HTTLPR/ rs25531 genotypes) and levels of neuroticism (as measured with the NEO-FFI) would predict rs-FC between amygdala and FFG, which may partly explain the described bias towards negative facial emotions. Second, we aimed to exploratory identify additional target areas with relation of amygdala rs-FC to variation in 5-HTTLPR/rs25531 genotype and associated trait neuroticism in subjects of European descend.

Study 2: Based on the coincidental observation in study 1 of amygdala rs-FC delineated subregions of the FFG, presumed to correspond to the face selective areas after applying GSR, we hypothesized the following: first, if amygdala rs-FC defined clusters do correspond to the commonly reported face sensitive areas in the FFG (i.e., FFA and OFA), then face sensitive areas as engaged by a face matching task should spatially map onto these rs-FC clusters. Second, if the effect of distinct amygdala rs-FC clusters is of neuronal origin, it should be possible to replicate this effect in independent subsamples of our data. Third, if the amygdala rs-FC defined clusters do correspond to distinct face sensitive areas, then they should show differential rs-FC connectivity patterns to other regions of the visual stream as well. Fourth, if amygdala defined rs-FC clusters correspond to face sensitive areas, then, given a hierarchical coupling between regions of the visual stream[78], we would expect the FFA cluster, as compared to the OFA cluster, to show decreases in rs-FC variance with the amygdala (as a potential indicator of rs-FC stability over time and thus closer coupling[79]).

Study 3: We aimed to develop a toolbox using the MATLAB computing environment that would combine features across multiple currently available toolboxes, such as the Brain Connectivity Toolbox, the Graph Analysis Toolbox, and the Network Based Statistic Toolbox (BCT[3]; GAT[80]; NBS[77]), and other mainly command-line based graph theoretical approaches to provide a comprehensive collection of graph analysis routines for analyses of functional brain connectivity in one single toolbox.

Methods

Study 1: *"5-HTTLPR/rs25531 polymorphism and neuroticism are linked by resting state functional connectivity of amygdala and fusiform gyrus."*[14]

Participants: 178 healthy volunteers of European descent from three different research centers participated in this study. Subjects with a history of psychiatric disorder and major neurological disease or first degree relatives with schizophrenia or mood disorder were excluded from the study. Participants completed the NEO Five Factor Inventory[81]. Sample characteristics in the entire sample and among genotypes are listed in Kruschwitz et al. (Table 1)[14]. Participants were recruited as part of a study on neurogenetic risk mechanisms for major mood disorders and schizophrenia[82,83] and were grouped according to their 5-HTTLPR/rs25531 expression into three groups[84]: homozygous for the l-allele with A at rs25531 (i.e., l_A/l_A), homozygous for the s-allele (i.e., s/s), and intermediate genotypes (i.e., s/l_A, s/l_G, l_G/l_G, l_A/l_G) (see Table 1 in Kruschwitz et al.[14] for distributions of genotypes grouped according to their expression). Genotype frequencies in this sample did not depart from Hardy-Weinberg equilibrium.

fMRI data: For each subject 150 gradient echoplanar imaging (EPI) volumes were acquired with standardized protocols at identical 3T Siemens Trio scanners in Berlin, Bonn and Mannheim during a 5 minutes scanning session (scanning parameters: number of slices=28, slice thickness=3 mm, interslice gap=1 mm, matrix size=64×64, flip angle=80°, TR=2 s, TE=30 ms). Participants were instructed to relax, keep their eyes closed, and not fall asleep. All volumes underwent slice timing, realignment, normalizing (standard EPI template, 3x3x3mm voxels) and smoothing (8mm FWHM) procedures. The data were detrended and band-pass filtered (0.01–0.08 Hz). A multiple-regression was performed on the data to remove possible sources of artifacts (six movement parameters, global mean signal, cerebrospinal fluid signals, white matter signals). Single-subject data processing was performed using DPARSF[85]. Second-level group analyses were performed using the statistical parametric-mapping software package SPM8 (http://www.fil.ion.ucl.ac.uk/spm).

Analysis of 5-HTTLPR/rs25531 modulated amygdala rs-FC: Left and right amygdala were separately defined as AAL-atlas volume-based seed regions to determine rs-FC of the amygdala (voxel-wise whole-brain correlations). Subsequently, whole-brain analyses of variance (ANOVA) were performed to determine brain areas with an association of amygdala rs-FC and 5-HTTLPR/rs25531 genotypes. An initial voxel threshold of $p<.001$ uncorrected was chosen and

clusters were retained exceeding 10 contiguous voxels[86]. Additionally, whole-brain family wise error (FWE) correction with p<.05 was applied to test whether results would hold under more conservative criteria. Individual rs-FC values for each significant area (average rs-FC: peak voxel with 3mm sphere) were extracted to determine specifically how genotypes contributed to the observed associations.

Relationship of NEO-FFI neuroticism score to 5-HTTLPR/rs25531 and amygdala rs-FC: Due to the assumed association of the s-allele to anxiety related traits as neuroticism[42,44], we tested for this association in our sample with a two-sample t-test (one-sided; p<.05) between s/s-homozygotes and l_A/l_A-homozygotes including neuroticism score as dependent variable. To examine whether genetically determined effects in amygdala rs-FC would replicate with neuroticism as a behavioral correlate (as measured with the NEO-FFI), we performed region of interest (ROI) based regression analyses. Analyses within the FFG were performed using a functional FFG mask (see Kruschwitz et al.[14]), whereas other ROIs were defined with the AAL-atlas. For each ROI-based regression model, small-volume (FWE, p<.05) and Bonferroni correction was performed. To test for reliability of the association of neuroticism and amygdala rs-FC within the FFG across the three independent research sites, individual rs-FC values were analyzed for each site separately using correlational analyses. The variables age, gender, handedness, and (if applicable) site were included in the models as covariates of no interest in all analyses[38,87,88].

Study 2: *"Segregation of face sensitive areas within the fusiform gyrus using global signal regression? A study on amygdala resting-state functional connectivity."*[15]

Participants: A group of 276 healthy volunteers from three different research centers (extending the sample in Kruschwitz et al.[14] by 98 individuals) participated in this study (see Table 1 in Kruschwitz et al.[15] for sample characteristics).

fMRI data: Additionally to the resting-state scan as described in study 1[14], subjects completed an emotional face matching task[34,82,89,90]. Resting-state (150 volumes) and task-fMRI (130 volumes) data were acquired with the same parameters mentioned in study 1. rs-fMRI preprocessing steps were similar to study 1 (additionally without global mean signal regression). Task-fMRI data underwent slice timing correction, realignment, normalizing (standard EPI template, 3x3x3mm voxels) procedures and were smoothed with 8 mm FWHM. For resting-state fMRI, single subject data preprocessing was carried out using DPARSF[85]. Single subject data processing for

task-fMRI (described in detail in[82,89]) and second-level group analyses for both, resting-state and task-fMRI data were performed using SPM8. Sliding-window analysis of the resting-state data was carried out using the DynamicBC toolbox[79].

fMRI data analysis pathway: The *a-priori* defined analyses were originally conducted within the context of study 1 and repeated for study 2 with a larger sample size. Based on the observations in the *a-priori* analyses, effects were target to *post-hoc follow-up* analyses to determine their reliability and nature in more detail.

A-priori defined analyses: Left and right amygdala were separately defined as AAL-atlas volume-based seed regions to determine rs-FC of the amygdala (voxel-wise whole-brain correlations). One-sample *t*-tests were used to determine significant amygdala rs-FC within the functionally defined FFG mask ($p \leq .05$, FWE corrected). This analysis was also carried out for the resting-state data without global mean signal regression (GSR). Results obtained from this latter analysis underwent a stepwise increased thresholding, to test if an anterior-posterior distribution of clusters in the fusiform gyrus could be observed.

Post-hoc follow-up analyses: Fusiform face area (FFA) and occipital face area (OFA)[91,92] were defined by thresholding procedures with the face matching task-activation corresponding *T*-values. To test for the reliability of the effect of GSR, significant amygdala rs-FC was determined by one-sample t-tests in each of the research sites separately. To probe whether the observed segregation of positive versus negative FFG clusters would also be reflected in differential rs-FC of these clusters to other regions of the visual stream, voxel-wise whole brain correlational FC was computed for each cluster as a seed, whereas their rs-FC maps were subsequently entered into paired-sample *t*-tests (contrasts: FFA>OFA and OFA>FFA; FWE small-volume correction within a face processing related neurosynth mask; $p \leq .05$). Direction of FC effects was determined by extracted peak voxel activity (3mm sphere) in the significant ROIs. To test if amygdala rs-FC defined FFA and OFA clusters would also differ in their variance of rs-FC to the amygdala across time (potential indicator of differences in rs-FC stability[79] in a hierarchical face processing system), a sliding-window approach was performed (with different window-sizes), whereas resulting rs-FC variances were subject to group analyses (i.e., paired *t*-tests between variance of amygdala-FFA and amygdala-OFA rs-FC). The variables age, gender, handedness, and (if applicable) site were included in the models as covariates of no interest in all analyses[38,87,88,93].

Study 3: *"GraphVar: a user-friendly toolbox for comprehensive graph analyses of functional brain connectivity."*[16]

GraphVar was developed in MATLAB 2011a under the GNU General Public License v3.0. To include a comprehensive collection of graph analysis routines for analyses of functional brain connectivity in one single toolbox, we combined features across multiple currently available toolboxes, such as the Brain Connectivity Toolbox, the Graph Analysis Toolbox, and the Network Based Statistic Toolbox (BCT[3]; GAT[80]; NBS[77]).

Results

Study 1: *"5-HTTLPR/rs25531 polymorphism and neuroticism are linked by resting state functional connectivity of amygdala and fusiform gyrus."*[14]

Analyses revealed three areas with significant associations of 5-HTTLPR/rs25531 genotype and amygdala rs-FC. For left amygdala rs-FC, areas included the right posterior FFG (i.e., occipital face area; OFA) and the left posterior cingulate cortex (PCC), whereas effects for rs-FC of right amygdala were observed in the right anterior cingulate cortex (ACC) (see Table 2 in Kruschwitz et al.[14]). Post-hoc pairwise comparisons between genotypes revealed that effects within the OFA were mainly driven by relatively weaker rs-FC in s/s-homozygotes as compared to rs-FC strength in l_A/l_A-homozygotes and intermediate genotypes. A similar pattern with an inverse relation of left amygdala rs-FC strength to genotype group was observed in the left PCC, revealing relatively stronger rs-FC in s/s-homozygotes in this area. In contrast, genotype associated effects of right amygdala rs-FC in the right ACC were driven by differences in rs-FC between s/s - and l_A/l_A-homozygotes versus the intermediate genotypes (see Fig. 1a-c and Table 2 in Kruschwitz et al.[14]). When performing the whole-brain family wise error (FWE) correction method ($p<0.05$) no significant results were observed.

Analyses furthermore revealed that individuals identified as s/s-homozygotes relative to l_A/l_A-homozygotes showed significantly elevated neuroticism scores and that neuroticism scores obtained a significant positive association with rs-FC between the bilateral amygdala and the right OFA, as well as with rs-FC between the right amygdala and the left OFA (see Fig 2a-b and Table 3 in Kruschwitz et al.[14]). No negative association of trait neuroticism and amygdala rs-FC within the FFG, as well as any significant association between neuroticism and rs-FC in PCC and ACC was observed. Subsample specific analyses confirmed reliability of effects as revealed

by similar associations of rs-FC to neuroticism in all three independent research sites (see Table 4 in Kruschwitz et al.[14]).

Study 2: *"Segregation of face sensitive areas within the fusiform gyrus using global signal regression? A study on amygdala resting-state functional connectivity."*[15]

A-priori defined analyses: Analyses revealed positive amygdala rs-FC in the anterior FFG, whereas the posterior FFG was characterized by negative rs-FC with the amygdala seeds. The same analysis on the resting-state data without global signal regression did not result in the distinct patterns of different rs-FC polarity, only positive amygdala rs-FC within the entire FFG (see Fig.1b and Fig 1c in Kruschwitz et al.[15]).

Post-hoc follow-up analyses: Overlay and overlap analyses of the task-derived face sensitive areas (see Table 3, Table 4 and Figure 2 in Kruschwitz et al.[15]) and the resting-state connectivity results revealed that positive rs-FC in the anterior FFG corresponded to the FFA, while the negative rs-FC in the posterior FFG corresponded to the OFA (see Fig. 3 in Kruschwitz et al.[15]). Analyses of the three independent scanner sites revealed similar patterns of positive and negative amygdala rs-FC within the FFG (see Fig. 4 and Table 5 in Kruschwitz et al.[15]). Direct comparisons of amygdala rs-FC defined FFA and OFA clusters revealed stronger rs-FC coupling of FFA to the right posterior superior temporal sulcus (pSTS) and the limbic lobe surrounding the bilateral amygdala (including hippocampal and parahippocampal gyri), whereas the OFA showed stronger couplings to the middle occipital gyrus (see Fig. 5 and Table 6 in Kruschwitz et al.[15]). Sliding-window analyses revealed that right amygdala rs-FC defined FFA and OFA differed significantly with respect of their rs-FC variance to the amygdala across time. Specifically, the FFA as compared to OFA showed significantly reduced rs-FC variance with the right amygdala (see Table 7 in Kruschwitz et al.[15]).

Study 3: *"GraphVar: a user-friendly toolbox for comprehensive graph analyses of functional brain connectivity."*[16]

GraphVar is a GUI-based toolbox that is freely available at www.rfmri.org/graphvar or www.nitrc.org/projects/graphvar and has already been downloaded over 2000 times since its first release. GraphVar does not require MATLAB programming experience and contains most functions included in the Brain Connectivity Toolbox, but allows users to add custom functions which can subsequently be accessed via the GUI. GraphVar accepts correlation matrices as input (or any n x n matrix containing information about connectivity among network nodes) but can also generate regular and dynamic time dependent connectivity matrices from input time series. Users may also provide demographic, clinical and other subject specific data for statistical analyses. GraphVar offers pipeline construction of a variety of graph networks with various methods. Additionally, GraphVar offers generation of subject specific "null-model networks and sub-network analyses". Network topological measures can be easily calculated, normalized, exported, and used in statistical analyses. Statistical analyses include correlation and partial correlation analyses and group comparisons (t-test, ANOVA) on the network measures but also on the raw connectivity matrices (i.e., network based statistics). Statistical tests can be performed in a parametric and non-parametric fashion (i.e., testing against null-model networks, non-parametric permutation testing) and include correction methods for multiple comparisons (Bonferroni correction and false discovery rate). In its latest version, GraphVar allows dynamic network analyses. If Matlab´s parallel computing toolbox is installed, GraphVar can distribute several jobs to different CPUs and thus speed up computation time. GraphVar offers an interactive viewer that allows intuitive exploration of statistical results, whereas these can easily be exported and reloaded. The program entails a detailed manual that includes usage instructions and a description of all the implemented functions, as well as various tutorials with sample data (see Kruschwitz et al.[16] for a schematic workflow of the toolbox (Fig. 1), for GraphVar´s setup interface (Fig. 2) and example outputs of the interactive results viewer (Fig. 3-6)).

Discussion

Using a multi-methodological approach across three studies, the work presented in this thesis aimed to explore and characterize different aspects of the brain´s intrinsic functional architecture as measured with rs-fMRI. As outlined in detail below (i) we demonstrate that variants of 5-HTTLPR/rs25531 genotype and different levels of neuroticism appear to be linked by rs-FC between amygdala and occipital face area, which in turn may partly account for altered processing of negative facial emotions; (ii) we provide initial evidence for the potential of amygdala rs-FC to segregate face-sensitive areas within the fusiform gyrus when global signal regression is applied; (iii) we developed "GraphVar" a user-friendly toolbox for comprehensive large-scale graph theoretical analyses of brain networks to facilitate future research on complex brain networks and their topology.

The brain´s intrinsic architecture I – *Effects of 5-HTTLPR/rs25531 polymorphism and neuroticism on functional connectivity of amygdala and fusiform gyrus*

We observed that s/s-homozygotes showed relatively weaker amygdala rs-FC with the posterior FFG as compared to rs-FC strength in l_A/l_A-homozygotes and intermediate genotypes (s/l_A, s/l_G, l_A/l_G). Specifically, s/s-homozygotes obtained rs-FC values near zero, indicating very weak rs-FC between amygdala and FFG, whereas the other genotypes showed comparably stronger negative rs-FC between these areas (see Kruschwitz et al.[14] for a discussion on 5-HTTLPR/rs25531 effects in PCC and ACC).

As discussed in more detail in Kruschwitz et al.[15], it remains an ongoing discussion if negative rs-FC can be interpreted straightforward as a marker of anti-correlated functional networks or whether they include components of artificially introduced polarity shifts after global signal regression. Regarding this ambiguity, it is possible to interpret effects within FFG as different amounts of feed forward functional association with the amygdala across genotypes. Subsequently, decreases in rs-FC for l_A/l_A-homozygotes and intermediate genotypes, as compared to s/s-homozygotes, could be interpreted as functioning more independent of congruent amygdala activations, either by a consequence of functional disentangled processes or by reverse regulatory effects. Thus, it could be speculated that the more negative rs-FC between amygdala and FFG observed in l_A/l_A-homozygotes and intermediate genotypes as compared to s/s-homozygotes may imply either an increased inhibitory influence between these two brain areas in l_A/l_A-homozygotes and intermediate genotypes (whereas s/s-homozygotes may obtain a diminished regulatory connection), or an increased functional coupling of these two areas in s/s-homozygotes.

The region where associations resided in this study falls within the OFA, which has been described as being a "core component" of the face processing system[78,92,94] and is suggested to be the first stage in a hierarchical face perception network[95]. Interestingly, task-fMRI research showed that this same region obtained greater neural responses in s-allele carriers as compared to l-allele carriers when performing a negative emotion face matching task[34]. Moreover, this previous study found that amygdala activity was significantly greater in s-carriers compared to l-homozygotes during the task. Hariri and colleagues[34] argued that their findings may possibly reflect an excitatory feedback from the amygdala to posterior FFG regions in s-allele carriers. Following this interpretation and the possible meaning of rs-FC polarity, it seems conceivable that the observed diminished negative rs-FC between amygdala and posterior FFG/OFA in s/s-homozygotes may indeed imply rather an increased co-activation in these individuals, possibly arising from increased importance of the excitatory feedback between amygdala and OFA. This suggestion corresponds with recent findings that showed that FFG activity is modulated by emotional expressions via signals from the amygdala during face perception[59,60,61,62].

These genetically determined associations replicated with neuroticism as a behavioral correlate as we similarly observed that individuals low in neuroticism as compared to individuals high in neuroticism showed stronger negative rs-FC between amygdala and FFG, whereas individuals high in neuroticism obtained a trend towards "more" positive rs-FC between amygdala and OFA. Applying the above-derived interpretation on these findings, it could be suggested that individuals high in neuroticism may obtain increased co-activation between these brain regions during rest. This finding can be interpreted in line with recent research that reported elevated amygdala activity[26,27,28] and elevated FFG activity[28] in response to negative emotional faces for anxiety related traits. Thus, similarly as for s/s-homozygotes, it may be hypothesized that a possibly reduced negative connectivity may partly account for biased processing of negative facial emotions in high neuroticism[23,24,25].

The brain´s intrinsic architecture II – *Segregation of face sensitive areas within the fusiform gyrus using global signal regression?*

During data analyses of study 1, we observed that, when applying global signal regression, distinct amygdala resting-state functional connectivity (rs-FC) clusters in the fusiform gyrus (FFG) appear to correspond to the commonly reported face sensitive areas: the occipital face area (OFA) as defined by negative amygdala rs-FC and the fusiform face area

(FFA) as defined by positive amygdala rs-FC. Effects observed in this current study corroborate the findings of Roy et al.[96], who examined whole-brain rs-FC of the amygdala while using GSR and reported positive rs-FC in the FFG, as well as negative rs-FC in the occipital cortex. Most importantly, our study extends these general findings by providing several lines of evidence (i.e., overlap with task-fMRI derived face sensitive areas, differential rs-FC to areas of the visual stream, temporal distinction with respect to the rs-FC variance over time) that the borders of these correlation-defined clusters may map on FFA and OFA. Although it remains debatable if anti-correlations following global signal regression are artificial or not (e.g., Wong et al.[97] and Chai et al.[98] provided evidence for the existence of anti-correlations without global signal regression), previous methodological studies[65,66,67] addressed the question how to interpret negative rs-FC as a byproduct of global signal regression (i.e., negative rs-FC as a marker of anti-correlated behavior between two regions versus an artificially introduced result of global signal regression). Specifically, regression against the global mean signal has been shown to obtain the potential to shift correlation distributions towards a mean correlation value close to zero, thereby artificially introducing negative correlations[65,66]. On the other hand, this artificial "zero-centering" method may also help by pulling apart neighboring, but functionally distinct, brain regions based on the FC distribution. In line with this, these anti-correlations appear to be spatially specific, and, most importantly, are reproducible while potentially resembling neurophysiologically relevant relationships between regions and networks – for example, the default-mode network[67,99]. Furthermore, it has been argued that GSR may also remove a true shared covariation in firing rate (i.e., a true global neuronal signal), thereby revealing relationships of neuronal populations otherwise masked by the dominant global signal[67,68,69]. Consistent with this idea, Keller et al.[69] demonstrated that both positive and negative BOLD correlations have neurophysiological correlates reflected in fluctuations of spontaneous neuronal activity, which led the authors to conclude that GSR likely reveals more than it obscures. Although these arguments make it difficult to attach a functional significance to these anti-correlations, our results do suggest that global signal regression may delineate regions in a functionally meaningful way, indicating that splitting the correlation distribution (of, in this case, the amygdala) into positive (FFA) and negative (OFA) correlation values may correspond to an underlying difference in function (see Kruschwitz et al.[15] for a discussion on the observed differential association with other regions of the visual stream). More generally, this opens up the possibility that rs-fMRI data with GSR applied may serve as a method to segregate functionally distinct areas in other functional domains as well.

The brain´s intrinsic architecture III – *Comprehensive graph analyses of functional brain connectivity with "GraphVar"*

"GraphVar" (www.rfmri.org/GraphVar) is a user-friendly graphical-user-interface (GUI)-based toolbox for comprehensive graph-theoretical analyses of brain connectivity including pipeline network construction and characterization, statistical analysis on network topological measures, network based statistics, and interactive exploration of results. We developed this toolbox with the aim of combining features across multiple currently available toolboxes, such as the Brain Connectivity Toolbox, the Graph Analysis Toolbox, and the Network Based Statistic Toolbox (BCT[3]; GAT[80]; NBS[77]) to provide a comprehensive collection of graph analysis routines for analyses of functional brain connectivity in one single toolbox (see Table 1 in Kruschwitz et al.[16] for comparison of global features of GraphVar with other published neuroscience graph analysis toolboxes that are freely available for research). With the development of GraphVar we intended to make graph theoretical analysis more readily available for a broader audience of neuroimaging researchers that was previously excluded from these methods due to a lack of sufficient scripting and programming experience, but whose research may benefit from graph-theoretical analyses. In its current form, GraphVar focuses on presently more established methods of analyses. However, we strive to continuously develop and update GraphVar to potentially include upcoming and emerging analysis methods of connectivity. These future developments may include the possibility of using voxel-wise brain connectivity or machine learning based classification with graph topological measures. We developed GraphVar under the GNU General Public License v3.0 with the hope that GraphVar will experience further developments also due to the help and engagement of committed community members (since its first release GraphVar already counts over 2000 downloads).

Concluding remarks – *From static networks to the brain´s dynamic nature*

The idea of the brain as a complex network has received a vast amount of interest in the past decade. However, only recently researchers have started to reason that it is not sufficient to characterize the brain as a static network but that it is important to acknowledge its dynamic nature as well. Specifically, to understand the nature of observed effects, one should acknowledge that during a single resting-state scan a region normally changes its connected counterpart(s) as a function of ongoing brain states[100], suggesting that observed effects in rs-FC are rather state-related. If translated to the presented results, different levels of functional

associations between the OFA, FFA, and amygdala as observed in study 2[15], could be interpreted as a consequence of differences in occurrences of states, where OFA and FFA are differentially recruited in the same network as the amygdala. This idea is supported by our data, as we observed a significant reduction in rs-FC variance of the amygdala with the FFA as compared to with the OFA over time[15]. As the variance of rs-FC time series may be interpreted as a proxy of how "stable" a connection between two areas is[79], it could be speculated that increases in rs-FC variance in the OFA (accompanied by decreases in rs-FC strength), as compared to the FFA, suggest a more independent functioning of this subregion to amygdala activations. Decreases in rs-FC variance in the FFA (accompanied by increases in rs-FC strength) could, on the other hand, indicate a closer coupling of FFA and amygdala during rest. This assumption is consistent with the idea that the neural system of face perception is hierarchically organized[78], where the OFA is suggested to be the first stage in this hierarchical face perception network[95], providing inputs to the FFA[78], which, in turn, projects and receives signals to and from the extended face processing system, including the amygdala[59,60,61,62]. Taking this idea into account, it may similarly be speculated that a possibly reduced negative rs-FC between OFA and amygdala in s/s-homozygotes (as compared to l_A/l_A-homozygotes and intermediate genotypes) and individuals high in neuroticism (as compared to low neuroticism)[14] may result as a consequence of a higher occurrence of state changes, where OFA and amygdala are more often assigned to the same network.

Based on these speculations, it becomes evident that it will be increasingly important to develop and incorporate new analysis methods to better understand the true (dynamic) nature of these and similar effects. Whereas this notion not only affected research on specific connections of single brain regions, it also recently started to influence methods that examine and characterize the overall structure of brain networks with graph analysis routines[101]. In the hope of contributing to these promising developments, we have incorporated a series of time-dependent network analyses methods in the latest "GraphVar" release - "DynamicGraphVar". By providing a sliding-window approach[100] in "DynamicGraphVar", scientists are now able to easily compute and track dynamic network changes such as time-varying global and local network topology, or investigate flexible community assignments of brain regions by tracking their changing clustering with other regions.

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Statutory declaration

„Ich, Johann Kruschwitz, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „The brain and its intrinsic functional architecture – Investigations using resting-state functional magnetic resonance imaging“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o.) und werden von mir verantwortet. Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o.) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum	Unterschrift

Statement of authorship

Johann Kruschwitz hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1

Kruschwitz, J.D., Walter, M., Varikuti, D., Jensen, J., Plichta, M.M., Haddad, L., Grimm, O., Mohnke, S., Pöhland, L., Schott, B., Wold, A., Mühleisen, T.W., Heinz, A., Erk, S., Romanczuk-Seiferth, N., Witt, S.H., Nöthen, M.M., Rietschel, M., Meyer-Lindenberg, A., Walter, H. (2015). 5-HTTLPR/rs25531 polymorphism and neuroticism are linked by resting state functional connectivity of amygdala and fusiform gyrus. Brain Structure and Function, 220(4), 2373–2385.

Beitrag im Einzelnen:
Datenpflege, Datenverarbeitung, Datenauswertung, Literaturrundschau, Hypothesengenerierung, statistische Datenanalysen, Verfassen, Einreichen und Überarbeitung des Manuskripts im Peer Review-Prozess.

Publikation 2

Kruschwitz, J.D., Meyer-Lindenberg, A., Veer, I.M., Wackerhagen, C., Erk, S., Mohnke, S., Pöhland, L., Haddad, L., Grimm, O., Tost, H., Romanczuk-Seiferth, N., Heinz, A., Walter, M., Walter, H. (2015). Segregation of face sensitive areas within the fusiform gyrus using global signal regression? A study on amygdala resting-state functional connectivity: Segregation of Face Sensitive Areas Using Global Signal Regression? Human Brain Mapping, 36(10), 4089–4103.

Beitrag im Einzelnen:
Datenpflege, Datenverarbeitung, Datenauswertung, Literaturrundschau, Hypothesengenerierung, statistische Datenanalysen, Verfassen, Einreichen und Überarbeitung des Manuskripts im Peer Review-Prozess.

Publikation 3

Kruschwitz, J.D., List, D., Waller, L., Rubinov, M., Walter, H. (2015). GraphVar: A user-friendly toolbox for comprehensive graph analyses of functional brain connectivity. Journal of Neuroscience Methods, 245, 107–115.

Beitrag im Einzelnen:
Konzeptualisierung, Literaturrundschau, Programmieren, Beta-Testing, Verfassen, Einreichen und Überarbeitung des Manuskripts im Peer Review-Prozess.

Unterschrift des Doktoranden

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Original publications

Publikation 1

Kruschwitz, J.D.*, Walter, M.*, Varikuti, D., Jensen, J., Plichta, M.M., Haddad, L., Grimm, O., Mohnke, S., Pöhland, L., Schott, B., Wold, A., Mühleisen, T.W., Heinz, A., Erk, S., Romanczuk-Seiferth, N., Witt, S.H., Nöthen, M.M., Rietschel, M., Meyer-Lindenberg, A., Walter, H. (2015). 5-HTTLPR/rs25531 polymorphism and neuroticism are linked by resting state functional connectivity of amygdala and fusiform gyrus. Brain Structure and Function, 220(4), 2373–2385.

Impact Factor^{+}: 5.618

Publikation 2

Kruschwitz, J.D.*, Meyer-Lindenberg, A.*, Veer, I.M., Wackerhagen, C., Erk, S., Mohnke, S., Pöhland, L., Haddad, L., Grimm, O., Tost, H., Romanczuk-Seiferth, N., Heinz, A., Walter, M., Walter, H. (2015). Segregation of face sensitive areas within the fusiform gyrus using global signal regression? A study on amygdala resting-state functional connectivity: Segregation of Face Sensitive Areas Using Global Signal Regression? Human Brain Mapping, 36(10), 4089–4103.

Impact Factor^{+}: 5.969

Publikation 3

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Impact Factor^{+}: 2.025

* Diese Autoren teilen die Erstautorenschaft.
+ Die Angaben beziehen sich auf das Jahr 2014.

Publikation 1

Kruschwitz, J.D.*, Walter, M.*, Varikuti, D., Jensen, J., Plichta, M.M., Haddad, L., Grimm, O., Mohnke, S., Pöhland, L., Schott, B., Wold, A., Mühleisen, T.W., Heinz, A., Erk, S., Romanczuk-Seiferth, N., Witt, S.H., Nöthen, M.M., Rietschel, M., Meyer-Lindenberg, A., Walter, H. (2015). 5-HTTLPR/rs25531 polymorphism and neuroticism are linked by resting state functional connectivity of amygdala and fusiform gyrus. Brain Structure and Function, 220(4), 2373–2385.

doi: 10.1007/s00429-014-0782-0
http://dx.doi.org/10.1007/s00429-014-0782-0

Publikation 2

Kruschwitz, J.D.*, Meyer-Lindenberg, A.*, Veer, I.M., Wackerhagen, C., Erk, S., Mohnke, S., Pöhland, L., Haddad, L., Grimm, O., Tost, H., Romanczuk-Seiferth, N., Heinz, A., Walter, M., Walter, H. (2015). Segregation of face sensitive areas within the fusiform gyrus using global signal regression? A study on amygdala resting-state functional connectivity: Segregation of Face Sensitive Areas Using Global Signal Regression? Human Brain Mapping, 36(10), 4089–4103.

doi: 10.1002/hbm.22900
http://dx.doi.org/10.1002/hbm.22900

Publikation 3

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doi: 10.1016/j.jneumeth.2015.02.021
http://dx.doi.org/10.1016/j.jneumeth.2015.02.021

Curriculum vitae
Johann Kruschwitz

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

Publication list

Article with peer-review

Lueken, U., **Kruschwitz, J.D.**, Muehlhan, M., Siegert, J., Hoyer, J., Wittchen, H.-U. (2011). How specific is specific phobia? Different neural response patterns in two subtypes of specific phobia. NeuroImage 56, 363–372.

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Kruschwitz, J.D., List, D., Beck, S., Wolfensteller, U., Goschke, T., Walter. H. (2014). The good and the bad and the brain´s response to anticipating ambivalent future events. 20th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Hamburg (Germany).

Kruschwitz, J.D., List, D., Beck, S., Wolfensteller, U., Goschke, T., Walter. H. (2015). The good and the bad: the brain´s response to emotion regulation during anticipation of ambivalent future events. Dresden Symposium on Volitional Control (SFB940), Dresden (Germany).

Acknowledgements

Ich danke Prof. Dr. Dr. Henrik Walter,
dem Forschungsbereich Mind and Brain
und meiner Frau Franziska.