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Effects of a Genome-Wide Supported Psychosis Risk Variant on Neural Activation during a Theory-of-Mind Task

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Abstract

Schizophrenia is associated with marked deficits in theory of mind (ToM), a higher order form of social cognition representing the thoughts, emotions and intentions of others. Altered brain activation in medial prefrontal and temporo-parietal cortex during ToM tasks has been found in patients with schizophrenia, but the relevance of these neuroimaging findings for the heritable risk for schizophrenia is unclear. We tested the hypothesis that activation of the ToM-Network is altered in healthy risk allele carriers of the single nucleotide polymorphism rs1344706 in the gene ZNF804A, a recently discovered risk variant for psychosis with genome-wide support. 109 healthy volunteers of both sexes in Hardy-Weinberg-equilibrium for rs1344706 were investigated with functional magnetic resonance imaging during a ToM task. As hypothesized, risk carriers exhibited a significant ($p < 0.05$ false discovery rate, corrected for multiple comparisons) risk allele dose effect on neural activity in the medial prefrontal cortex and left temporo-parietal cortex. Moreover, the same effect was found in the left inferior parietal cortex and left inferior frontal cortex which are part of the human analogue of the mirror neuron system. Additionally, in an exploratory analysis ($p < 0.001$ uncorrected), we found evidence for aberrant functional connectivity between frontal and temporo-parietal regions in risk allele carriers. To conclude, we show that a dysfunction of the ToM-network is associated with a genome wide supported genetic risk variant for schizophrenia and has promise as an intermediate phenotype that can be mined for the development of biological interventions targeted to social dysfunction in psychiatry.

Keywords: Theory of Mind, Mentalizing, Schizophrenia, Imaging genetics, Medial prefrontal cortex

Introduction

In schizophrenia, a major, highly heritable disorder with concordance rates between identical twins of almost 50 %, the impact of a variety of candidate genes on the brain has been studied ¹. One useful strategy in this endeavour is imaging genetics, which uses neuroimaging techniques to identify structural or functional brain systems that mediate genetic vulnerability or liability to mental disorders ². In these neural intermediate phenotypes (or endophenotypes), due to their proximity to the genetic level, penetrance of genetic variation is expected to be higher, an assumption confirmed by recent meta analyses ^{3,4}. To identify neural systems linked to genetic risk, most studies in imaging genetics of schizophrenia have used neurocognitive probes, in particular working memory ⁵. The most consistent finding has been a dysfunction of the dorsolateral prefrontal cortex ^{2,6} which has been related to genetic variation in candidate genes such as COMT ⁷⁻⁹ or BDNF ¹⁰, as well as abnormalities in the connectivity of DLPFC ^{2,11}. The selection of candidate genes is based on prior data on particular genes, neural or neurotransmitter systems in schizophrenia. Supplementing this strategy, the recent emergence of large-scale systematic genome-wide association studies (GWAS), in which hundreds of thousands of single-nucleotide polymorphisms (SNPs) in large numbers of cases and controls are investigated, allows identification of novel risk variants which so far had not been implicated in the etiology of schizophrenia. In schizophrenia, a GWAS and follow-up analysis in over 20 000 individuals has shown strong evidence for association with susceptibility to schizophrenia for a common variant (rs1344706) in ZNF804A ¹². This finding has been replicated recently ¹³. Interestingly, this variant was also associated with a broad psychosis phenotype that included bipolar disorder ¹². Using an established neurocognitive probe, a two-back working memory task, we recently found that this variant is associated with function in the human brain: healthy carriers of risk alleles showed disturbed connectivity of the right DLPFC with left DLPFC and hippocampus ¹⁴, mirroring findings in patients with schizophrenia ¹⁵.

While cognitive tasks such as working memory reliably activate DLPFC and tap into neurocognitive functions disturbed in the disease, social dysfunction is a separable major predictor of adjustment and quality of life in schizophrenia ¹⁶, which is of major clinical importance. There is

accumulating evidence that social cognition is impaired in schizophrenia^{16, 17}, as well as in people at risk for schizophrenia¹⁸⁻²⁰ and that social cognitive deficits are independent of other neurocognitive deficits²¹⁻²³. More generally, the social brain hypothesis of schizophrenia^{24, 25} has put forward the idea that psychosis comes as a costly by-product of social brain evolution and thus is based on genetic factors supporting higher order social cognition. Only recently, the neurogenetics of social cognition is coming into focus within neurobiology²⁶. Since a variety of social functions is influenced by genetic variation²⁷ and deficits of social cognition have been observed in people at risk for schizophrenia¹⁸⁻²⁰ it appears reasonable to ask whether genetic risk for schizophrenia could operate through the domain of social information processing. However, in contrast to intensive work on neurocognition, the genetic impact on brain activity during higher order social cognition has not yet been investigated.

One especially well characterized uniquely human form of higher order social cognition is theory of mind (ToM), also called mentalizing. This is the ability to represent the mental states, i.e. the thoughts, emotions and intentions of others, an ability crucial for successful social interaction²⁸. The neural basis of mentalizing has consistently been characterized as a network including the dorsomedial prefrontal cortex (dmPFC), the superior temporal sulcus extending into the temporo-parietal junction (TPJ) and was sometimes found to include the temporal poles^{29, 30}. ToM has constantly been found to be impaired in schizophrenia as summarized by two recent metaanalyses comprising 29 ToM studies including 831 patients²³ and 36 ToM studies including 1181 patients³¹, respectively. ToM dysfunction has been used to explain persecutory delusions²², a key symptom of schizophrenia characterized by misattribution of intentions to others. Remarkably, impaired self-other-distinction is central to various other dysfunctions in schizophrenia like attributional bias³² and false action attribution³³⁻³⁵. Overall effects sizes for ToM deficits were large ($d = 1.21$) in non-remitted patients and less pronounced ($d = 0.80$) but still significant in remitted patients³¹. While specifics of ToM-deficits in schizophrenia may vary with specific psychopathology^{36, 37}, the fact that ToM deficits are even found in remission^{31, 38, 39} and in people at risk for schizophrenia¹⁸⁻²⁰ support the idea that impaired ToM is a trait marker of the

illness, indicating that the associated neural systems can be investigated as a candidate intermediate phenotype for schizophrenia.

Imaging studies on social brain dysfunctions in schizophrenia have identified the medial prefrontal cortex, the amygdala and the inferior parietal cortex as key regions of interest ⁴⁰. To date, brain activation studies using ToM-tasks in schizophrenia are few, comprising until recently two PET ⁴¹, ⁴² and one fMRI study ⁴³. Another fMRI study also found neural abnormalities during ToM in participants with high genetic risk ⁴⁴, further strengthening the case for this system as an intermediate phenotype. These studies found reduced activation in patients in either right ⁴¹ or left inferior ⁴² or bilateral ⁴⁴ prefrontal cortex or in a cortico-cerebellar circuit (left PFC, right cerebellum) ⁴³. Adding to these studies, we recently investigated a group of patients with paranoid schizophrenia ⁴⁵ using a ToM-cartoon paradigm during fMRI ^{46, 47}. Two key regions of the ToM Network were significantly less activated in the patient group, namely the dorsomedial prefrontal cortex and the temporo-parietal cortex bilaterally.

Based on the social brain hypothesis of schizophrenia and the consistent ToM deficits in schizophrenia we set out to test the hypothesis that the neural network supporting ToM would show aberrant activations in healthy carriers of the first recently identified risk variant with genome wide support, rs1344706 ¹². We used a variant of our previously published ToM-cartoon paradigm including a ToM condition where subjects had to judge the affective state of the protagonist and a control condition where subjects had to count the number of living beings. Based on our prior studies in schizophrenia ⁴⁵, we specifically postulated to find dysfunctions in the dorsomedial prefrontal cortex and the temporo-parietal cortices. Moreover, since we found pronounced genotype-dependent abnormalities in functional connectivity of the right dorsolateral prefrontal cortex (dlPFC) with other brain regions in our previous study ¹⁴, we performed an exploratory analysis of functional connectivity using as seed regions the right dlPFC along with the two aforementioned a priori regions of interest.

Methods

Subjects. As part of an ongoing study of the genetics of schizophrenia and bipolar disorder ¹⁴, 51 healthy German volunteers with parents and grandparents of European origin were recruited at Bonn and 58 at Mannheim. The reported sample is a subsample of the one reported in Esslinger et al 2009 ¹⁴. No participant had lifetime or family history of schizophrenia or affective disorder, 18 were rs1344706 CC homozygotes, 49 CA heterozygotes and 42 AA homozygotes (in Hardy-Weinberg Equilibrium ($\chi^2 = 0.33$, $df = 1$, $p = 0.57$; C = Cytosine, A = Adenine = risk allele)). Gender, age, handedness and level of education did not differ significantly between genotype groups (Suppl. Tab. 1). There was no significant correlation between the distribution of risk alleles and gender, age or scan site (all correlations $r < 0.085$). Subjects gave written informed consent. The study was approved by the local ethics committees of the universities of Bonn and Heidelberg.

Theory-of-Mind-Task: The experimental task (480 sec) was presented as part of a functional imaging genetics battery during a 1 hour scan session and consisted of two alternately presented conditions, a ToM (mentalizing) condition and a control (non-mentalizing) condition. In this improved version of a previously published paradigm from our group ^{45, 47} each of the 8 trials/condition was introduced by an instruction (6.53 sec) followed by a cartoon story (22.58 sec) in 3 consecutive pictures (7.53 sec/picture). All pictures were free of direct signs of the characters' emotions like facial expressions. As indicated in the preceding instruction test subjects had to judge picture-to-picture changes either in the number of living beings shown (control condition) or changes in affective states of the protagonist (ToM condition) by pressing a button (see Suppl. Fig. 1). In a pilot study in 21 healthy controls (Schnell et al., in preparation), we verified that this task robustly activates the ToM network including our a priori regions of interest, the dorsomedial prefrontal cortex and the temporo-parietal cortex.

DNA-extraction and genotyping: Genomic DNA was prepared from whole blood according to standard procedures. Rs1344706 was genotyped using a TaqMan 5' nuclease assay. Accuracy was assessed by duplicating $n=24$ ($> 15\%$) of the original sample. No genotyping errors were observed.

Imaging parameters. BOLD fMRI was performed on two Siemens Trio 3T scanners at the Central Institute of Mental Health Mannheim and the Life and Brain Center at the University of Bonn. At both sites identical sequences and scanner protocols were used. Quality assurance (QA) measures were conducted on every measurement day at both sites according to a multicenter QA protocol revealing stable signals over time. To stringently account for any differences in signal-to-noise across sites, site was used as a covariate of no interest for all statistical analyses. We used an echoplanar imaging (EPI) sequence (240 whole brain scans, TR 2s, TE 30ms, 80 degrees flip angle, 28 slices of 4 mm thickness plus 25 % gap, 3x3mm in plane resolution of 64x64 voxels, descending slice order).

Data analysis: In the analysis of functional data with SPM5 (www.fil.ion.ucl.ac.uk/spm) preprocessing included realignment, normalisation to a standardized EPI-template, and smoothing with a Gaussian kernel of 9mm (full width at half maximum). Subsequent statistical parametric analysis comprised two steps. The first level model included five epoch regressors i.e. a regressor for stories and instructions for both experimental conditions and one regressor for all button presses, as well as six regressors modelling head-movement parameters. At the group level, individual first-level contrasts (mentalizing > control) were entered in a one-sample-T-test to analyse the main effect with site as a covariate of no interest. Genotype effects were assessed using a regression analysis with number of risk alleles as regressor with site as a covariate of no interest. For imaging results, significance threshold was set to $p < 0.05$ (FDR, false discovery rate), corrected for multiple voxel-wise comparisons across the whole brain. We have previously demonstrated that this procedure is conservative in imaging genetics ⁴⁸.

Functional Connectivity analyses: We analysed functional connectivity for three seed regions, our two a priori regions of interest in which we actually observed a risk allele dose effect, i.e. left TPJ and dmPFC, as well as the right dlPFC, where abnormal connectivity during working memory was found in our previous study ¹⁴. The preprocessing for the analysis of functional connectivity with SPM5 included realignment, slice-timing and normalisation to a standardized EPI-template and smoothing with a Gaussian kernel of 9mm (full width at half maximum). Subsequent statistical analysis comprised two subsequent estimations of first level models. In the first step an individual first level model including five experimental regressors and the six head movement covariates was estimated for every subject according to the procedure described in the previous paragraph.

For timeseries extraction from the right dlPFC, an anatomical dlPFC mask was imposed a priori and adopted from our previous analysis of connectivity effects during a working memory task (AAL: BA 9, 46 with exclusion of the medial brain surface) ¹⁴. Within this mask the sphere was centred on the regional maximum of the mentalizing effect in each individual subject and individual timeseries using the first eigenvariate of all voxels surpassing a nominal threshold of $p = 0.025$ (ToM > control condition) were extracted within a sphere of 6mm radius. The nominal threshold was used to exclude noise from the timeseries and not used for statistical inference. For assessment of functional connectivity within the ToM network (TPJ, dmPFC), spheres for timeseries extraction were centred in the maxima of the functional main effect (ToM > control condition) in the dmPFC [-6 54 39] and the left TPJ [-54 -57 30]. In order to avoid covariation of voxels with the seed timeseries due to task activation, all task related variance was subtracted from the seed voxel time series. Contribution of signal changes in the white matter (WM) and cerebrospinal fluid (CSF) was controlled by extraction of averaged time series from WM and CSF-masks. In the second step, the dlPFC time series was used as the covariate of interest in a new first level model for every subject i.e. it was added to the five experimental regressors, the WM- and CSF-regressors and the six head movement covariates. Finally, the resulting individual contrast images entered a second level whole brain regression analysis to test for genotype effects on functional connectivity by using the number of risk alleles as a regressor. Site was used as a covariate of no

interest. For this exploratory analysis, significance threshold was set to $p < 0.001$ uncorrected, with a clustersize of $k \geq 10$ voxel.

Results

Behavioural data: There was a clear effect of condition with more errors and longer reactions times for the ToM compared to the control condition, but no risk allele dose effect on either (Tab. 1).

Neuroimaging data: Confirming our previous work, we found a strong and significant main effect ($p < 0.01$, FWE (family wise error) corrected for multiple comparison across the the whole brain), comparing the ToM with the control condition in the ToM network comprising prefrontal cortex, precuneus/posterior cingulate, temporal and parietal cortex (Fig. 1, green colors, see also Suppl. Tab. 2).

Genotype strongly impacted on processing in this network (Fig. 1, red colors, Fig. 2, Tab. 2): as hypothesized, we found a clear parametric effect of genetic load ($CC > AC > AA$; A = risk allele) in key areas for ToM, the dorsomedial prefrontal cortex and left temporo-parietal cortex as well as in left inferior parietal cortex, posterior cingulate and left lateral prefrontal cortex. All genotypes effects were significant at a stringent level of $p < 0.05$ FDR (false discovery rate)-corrected for multiple comparisons across the whole brain.

Genotype also impacted on functional connectivity in our exploratory analysis using an uncorrected level of $p < 0.001$ in two regions (Tab. 3). For the left TPJ, we observed a positive correlation of risk allele number and functional connectivity with the left inferior frontal gyrus, as well as with the left cuneus, left caudate and right thalamus, i.e. increased connectivity in risk allele carriers. For the right dlPFC, we found a negative correlation of risk allele number and functional connectivity with left posterior TPJ adjacent to the risk-allele related effect on TPJ activation during mentalizing in the categorical analysis, as well as with the left secondary visual cortex in the lingual gyrus ($p < 0.001$, uncorrected), i.e. decreased connectivity in risk allele carriers.

Discussion

In the present study we investigated genetic effects of a genome-wide supported psychosis risk variant, the single nucleotide rs1344706 in the gene ZNF804A, on brain activation during a ToM task.

Confirming our hypothesis, we found a significant risk allele dose effect in parts of the ToM-network, i.e. the dorsomedial PFC and the left temporo-parietal junction, as well as in left inferior parietal cortex and left inferior prefrontal cortex, i.e. in the human analogue of the mirror neuron system. These findings are consistent with previous results in patients with schizophrenia. Furthermore, we found evidence for aberrant connectivity between frontal and temporo-parietal areas in risk allele carriers.

Behavioural results

We found no behavioural differences between healthy risk and non-risk carriers, neither on performance, nor on reaction times. This result conforms to our general experience with imaging genetics tasks (including with the present variant ¹⁴) that are optimized for reliable neural activation, not behavioural sensitivity. A possible explanation for this divergence of neural differences between genotypes with a lack of behavioral differences is that behavioural parameters are biologically more distal to genes than brain activation, although greater genetic than behavioural effects are not certain as has been discussed recently ⁴⁹

Risk allele dose effect within dorsomedial PFC and left temporo-parietal-junction

In accordance with our a priori hypothesis we found a significant risk allele dose effect on brain activation comparing the ToM (mentalizing) and the control condition (no mentalizing) in dorsomedial prefrontal cortex and the left temporo-parietal junction, as well as in the posterior cingulate cortex. This risk allele dose effect was clearly overlapping with the main effect of ToM (see Fig. 1). Both, the left temporo-parietal junction ⁵⁰ as well as the dorsomedial prefrontal cortex have been described as the most specific regions involved in ToM ⁵¹. Moreover, the left TPJ has been found to be particularly

involved in representing mental states in a social context⁴⁶. In our recent study in patients with schizophrenia, these two regions, dmPFC and TPJ, showed significantly reduced activation comparing the ToM with the control condition⁴⁵.

Risk allele dose effect within the left inferior prefrontal and parietal cortex

We also found a risk allele dose effect in the left inferior prefrontal cortex and the left inferior parietal cortex. In principle, these findings might be related to the well-known executive deficits associated with prefrontal cortex dysfunction that have been described as one of the hallmarks of neurocognitive dysfunction in patients with schizophrenia and in subjects at risk for schizophrenia^{6, 52}. However, this interpretation is unlikely since we previously examined the effects of rs1344708 on brain activation during working memory in an overlapping sample and found no regional categorical activation differences¹⁴. We therefore propose that the present findings are specifically related to social information processing investigated in the present task, namely the representation of mental states, i.e. mentalizing. Both regions have been described as activated in theory of mind tasks^{47, 53, 54}. In agreement with this, we have recently found for another candidate gene risk variant for schizophrenia that pleiotropic effects in DLPFC are depending on the (emotional vs. cognitive) content of the information processed³.

In schizophrenia the left inferior prefrontal cortex has been observed to be significantly less activated in a ToM study⁴³. Also, aberrant activation of the left inferior parietal cortex has been found in schizophrenia to be involved in the misrepresentation of actions and intentions of others^{34, 35}. More specifically, activation in the inferior left parietal cortex during a task in which subjects had to monitor own and external motor intentions, correlated with a certain type of psychopathology, i.e. passivity phenomena, the experience of alien control over self initiated movements³⁴. Therefore, our findings are in accordance with involvement of this region in the psychotic misattribution of intentions. Further support comes from a very recently published study showing that intracranial electrical stimulation of the left inferior parietal cortex results in the feeling of having carried out a movement intention even if there

wasn't any movement⁵⁵. This is direct evidence that the left parietal cortex is causally involved in the representation of intentions, which are misattributed in patients with positive symptoms of schizophrenia⁵⁶.

Of note, human neuroimaging studies showed combined activation of the left inferior prefrontal cortex and left inferior parietal cortex when observers of actions have to infer the intentions behind the actions^{57, 58}. Therefore, these two regions have been postulated to be the human analogue of the so called mirror neuron network, a basic system for intention detection in non-human primates^{58, 59}. However, it should be stressed that the existence of a mirror neuron system in humans is not yet proven – recent neuroimaging studies have called it's existence in question^{60, 61}.

In summary, all regions showing a risk allele dose effect in our study have been described to be involved in either theory of mind or intention representation in healthy subjects and found to be dysfunctional in studies of schizophrenia. Therefore, the pattern of aberrant brain activation found in healthy carriers of risk alleles is a promising neurofunctional endophenotype for schizophrenia.

Connectivity analysis

Our exploratory analysis provided evidence for aberrant functional connectivity between prefrontal and posterior temporo-parietal areas with a mix of decreased connectivity (between right DLPFC and left posterior temporal cortex) as well as increased connectivity (between left TPJ and left inferior PFC). Although no strong conclusions can be drawn from these results as they were found only on an uncorrected level, we would like to suggest a tentative explanation. Our findings may be interpreted by reduced top-down-influence of the DLPFC on the posterior TOM system, possibly compensated by increased connectivity between the posterior parts of the TOM system and the inferior PFC as part of the mirror neuron system. Moreover, a disturbed top-down modulation through DLPFC could be one convergent mechanism for psychosis across the Kraepelinian categories, i.e. for schizophrenia as well as bipolar disorder, as behavioural ToM deficits have also been found in symptomatic⁶² and euthymic

^{63, 64} bipolar patients. Notably bipolar patients, especially those with persecutory delusions, show structural abnormalities in DLPFC similar to those in patients with schizophrenia ⁶⁵.

Moreover, although we did not find the same regions to be dysfunctional in this study and our previous study using an n-back task, the fact that the same SNP in ZNF 804A impaired neurocognitive probes in a social cognition as well as in an executive tasks suggests that social cognition and executive function are not totally independent from each other.

Molecular mechanisms

While our findings establish that genetic variation in ZNF804A or in close linkage equilibrium is functional in human brain, the molecular mechanisms underlying these systems-level findings are presently unknown. It has been speculated that the dopaminergic and serotonergic systems might contribute to ToM deficits ⁶⁶. However, the best known candidate molecules involved in social cognition at the moment have been described in the domain of neuropeptides like oxytocin and vasopressin ^{67, 68}. Interestingly, oxytocin has been shown recently to improve theory of mind function in healthy controls ⁶⁹. Moreover, oxytocin has been demonstrated to alter the visual scanning of stimuli in social interaction ⁷⁰, a crucial element in ToM tasks. While ZNF804A is predicted to be a regulatory protein, there is no positive evidence for a regulatory effect of ZNF804A in these signalling cascades yet, which we, based on our finding, consider as an interesting subject for further studies.

Limitations

Compared to genome wide studies of behavioural phenotypes, the number of subjects included in our study is considerably smaller. However, our sample size of 109 subjects is supported by convergent evidence from two recent meta-analysis indicating that sample sizes above 60-70 provide adequate power in imaging genetics ^{3, 4} which is consistent with our previous own recommendations ⁴⁸ While for different genetic variants, effect sizes and therefore sample sizes would certainly be expected to vary, our current observation of a strong genetic effect for rs134470 on the ToM imaging phenotype further

indicates that penetrance of common genetic variants on the level of functional neuroimaging is higher than for categorical disease phenotypes and allows for sample sizes of around 100 participants.

Conclusion

We provide the first evidence for a genetic contribution to the neural network supporting theory of mind functions involving the representation of mental states of others, linking dysfunction in this network to genetic risk for schizophrenia. While the underlying molecular mechanisms remain to be uncovered, our results identify an intermediate phenotype that can be mined for the development of biological interventions targeted to social dysfunction in schizophrenia.

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Conflict of interest: The authors declare no conflict of interest.

Supplementary information is available at the website of Molecular Psychiatry

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Figure legends

Fig. 1: Functional risk allele dose effect (red-yellow) superimposed on main effects of mentalizing (green)

Green: categorical main effect of ToM > control condition across all subjects ($p < 0.01$ FWE for display reasons, $n = 109$, see also S1). Superimposed in red/yellow: colour coded risk allele dose effect ($p < 0.05$ FDR = false discovery rate, corrected for multiple comparisons across the whole brain).

Fig. 2: Effect sizes for risk allele dose effect

Scatter plots of effect sizes for risk allele dose effect for three regions (black bar = median) at the indicated coordinates. C = cytosine, A = adenine = risk allele; r. MPFC = right medial prefrontal cortex; l. IPL = left inferior parietal cortex, l. TPJ = left temporo-parietal junction.

Table legends

Table 1: Behavioral results

Reaction times (RT) and number of errors were significantly higher in the ToM condition (n = 109). The number of risk alleles had no significant effect, neither on reaction times nor on errors. RT = Reaction Times; s = seconds; s.d. = standard deviation; T = t-value; P = p-value; df = degrees of freedom; ANOVA = analysis of variance

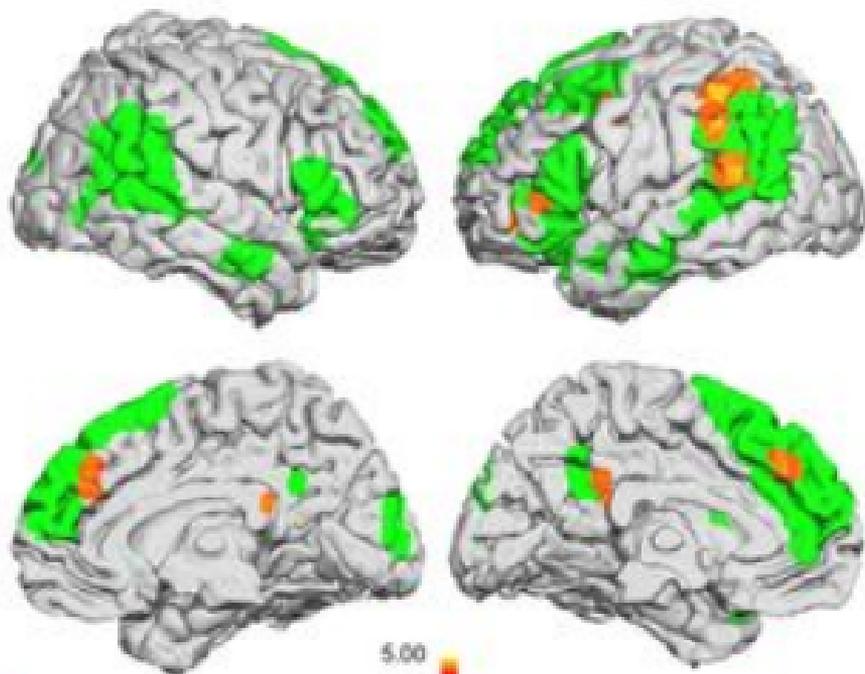
Table 2: Risk allele dose effect on regional brain activation

Regions showing a significant effect ($p < 0.05$ FDR-corrected across the whole brain, cluster-size $k > 10$ voxels) of the number of risk alleles on the magnitude of functional difference between ToM and control condition assessed with SPM whole brain regression analysis (n = 109). L = left, R = right, MNI coords. = Montreal Neurological Institute (MNI) space coordinates, x, y, z = location in mm with the three axes; k = number of voxels; P = p-value; FDR = False discovery rate; T = t-value; Z = z-value; dmPFC = dorsomedial PFC, dlPFC = dorsolateral PFC, vlPFC = ventrolateral PFC, TPJ = temporoparietal junction; IPL = inferior parietal lobe, pCC = posterior cingulate cortex.

Table 3: Risk allele dose on functional connectivity

Brain regions showing a significant correlation between the # (number) of rS1344706 risk alleles and the functional connectivity of brain regions with the indicated seed regions of the connectivity analysis in left dmPFC, left TPJ and right dlPFC, assessed with second level SPM whole brain regression analysis of first level functional connectivity maps with number (#) of risk alleles (n = 109, $p < 0.001$, uncorrected, clustersize $k \geq 10$ voxel). L = left, R = right, MNI coords. = Montreal Neurological Institute (MNI) space coordinates, x, y, z = location in mm with the three axes; k = number of voxels; P = p-value; T = t-value; Z = z-value; dlPFC = dorsolateral PFC, TPJ = temporo-parietal junction.

BOLD-Effect: Mentalizing>Control Condition

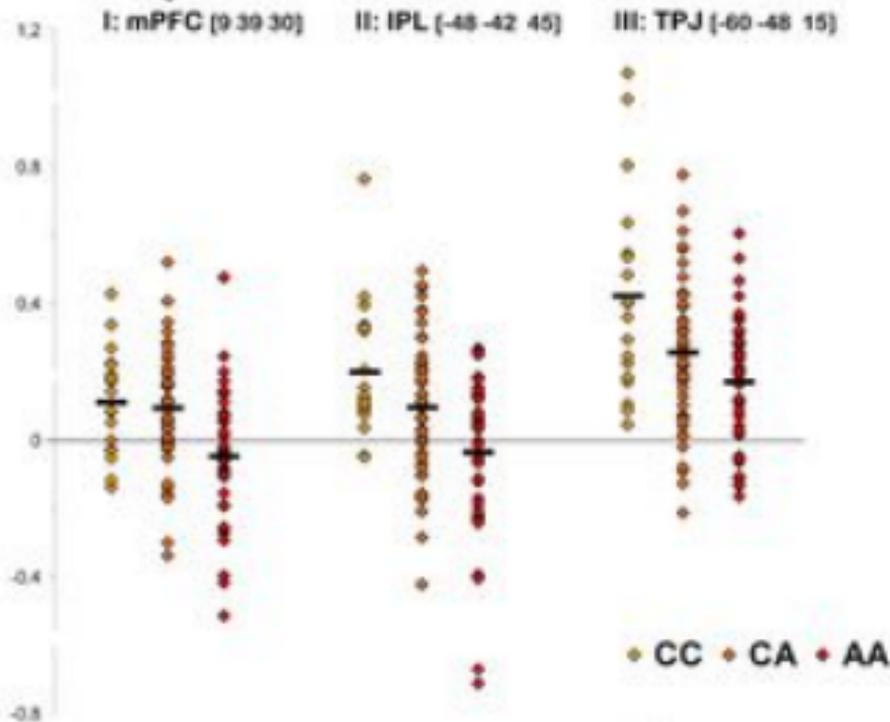
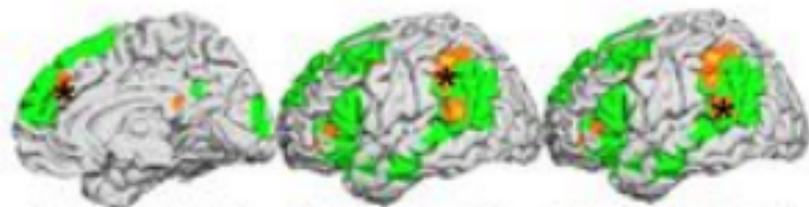


Main Effect
 $p < 0.01$ FWE corr.

5.00
2.00
-2.00
-5.00

**Effect of rs1344706
allele number**
 $p < 0.05$ FDR corr.

Regional effects of rs1344706 allele number on functional activation



Descriptive		mean	s.d.					
RT [s]	Mentalizing Condition	3.031	0.696					
	Control Condition	2.470	0.588					
Errors	Mentalizing Condition	1.826	1.413					
	Control Condition	1.055	1.145					
Main Effect of Condition: Paired t-test (one-tailed)				mean	s.d.	df	T	P
RT [s]	Mentalizing-Control Condition		0.562	0.502	108	11.684	<0.001	
Errors	Mentalizing-Control Condition		0.771	1.244	108	6.465	<0.001	
ANOVA: Effect of rs1344706 genotype					df	F	P	
RT [s]	Mentalizing Condition			2	2.007	0.139		
	Control Condition			2	1.607	0.205		
	Difference			2	0.428	0.653		
Errors	Mentalizing Condition			2	1.063	0.349		
	Control Condition			2	0.593	0.554		
	Difference			2	2.257	0.110		

Table 1

Lobe	Region	Structure	MNI coords. x,y,z [mm]			Cluster -size k	T	Z
Frontal Lobe	vIPFC	L. Middle Frontal Gyrus	-39	42	-6	82	4.29	4.11
	dIPFC	L. Inferior Frontal Gyrus	-30	33	-12		4.16	3.99
	dmPFC	R. Medial Frontal Gyrus	9	39	30	74	4.08	3.93
	dmPFC	L. Medial Frontal Gyrus	-6	39	36		4.03	3.88
	dIPFC	L. Precentral Gyrus	-51	0	30	41	4.07	3.91
	dIPFC	L. Middle Frontal Gyrus	-51	6	39		3.82	3.69
	dIPFC	L. Middle Frontal Gyrus	-42	24	24	15	3.68	3.56
Temporal Lobe	TPJ	L. Superior Temporal Gyrus	-60	-48	15	53	4.30	4.12
Parietal Lobe	IPL	L. Inferior Parietal Lobule	-48	-42	45	164	5.25	4.94
	IPL/TPJ	L. Supramarginal Gyrus	-60	-45	36		4.18	4.01
	IPL	L. Inferior Parietal Lobule	-45	-54	51		3.92	3.78
	pCC	L. Posterior Cingulate	0	-39	21	19	3.81	3.68
	pCC	L. Posterior Cingulate	-6	-42	33		3.54	3.44

Table 2

	Lobe	Structure	MNI coords. x,y,z [mm]	Cluster- size k	T	Z
Functional connectivity between left dmPFC [-6 54 39] and other brain regions						
<i>No significant correlations in any brain region with # of risk alleles</i>						
Functional connectivity between left TPJ [-54 -57 30] and other brain regions						
<i>Positive correlation with # of risk alleles</i>	Frontal Lobe	L. Inferior Frontal Gyrus	-54 9 30	19	3.77	3.65
	Occipital Lobe	L. Cuneus	-18 -78 9	12	3.76	3.64
	subcortical	R. Thalamus	18 -30 18	12	3.68	3.56
		L. Caudate Tail	-24 -33 15	31	3.96	3.81
Functional connectivity between right DLPFC (anatomic mask) and other brain regions						
<i>Negative correlation with # of risk alleles</i>	Frontal Lobe	R. Precentral Gyrus	33 -6 36	25	4.27	4.10
	Temporal Lobe	L. Middle Temporal Gyrus	-45 -75 18	26	3.32	3.23
	Occipital Lobe	L. Lingual Gyrus	-18 -90 -12	25	3.83	3.70

Table 3