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CACNA1C risk variant affects microstructural connectivity of the amygdala

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ABSTRACT

Deficits in perception of emotional prosody have been described in patients with affective disorders at behavioral and neural level. In the current study, we use an imaging genetics approach to examine the impact of *CACNA1C*, one of the most promising genetic risk factors for psychiatric disorders, on prosody processing on a behavioral, functional and microstructural level. Using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) we examined key areas involved in prosody processing, i.e. the amygdala and voice areas, in a healthy population. We found stronger activation to emotional than neutral prosody in the voice areas and the amygdala, but *CACNA1C* rs1006737 genotype had no influence on fMRI activity. However, significant microstructural differences (i.e. mean diffusivity) between *CACNA1C* rs1006737 risk allele carriers and non carriers were found in the amygdala, but not the voice areas. These modifications in brain architecture associated with *CACNA1C* might reflect a neurobiological marker predisposing to affective disorders and concomitant alterations in emotion perception.

1. Introduction

Correct interpretation of emotional signals is crucial for successful social interactions. In the acoustic domain, socially relevant cues can be expressed verbally (semantic information) and nonverbally by modulation of speech melody (prosody). Nonverbal communication enables inferences about the emotional state of the speaker and it has been demonstrated that perception of emotional prosody is impaired in several psychiatric disorders including schizophrenia (SCZ, (Bozikas et al., 2006; Gold et al., 2012; Hoertnagl et al., 2014), bipolar disorder (BD, (Bozikas et al., 2007; Hoertnagl et al., 2014), major depressive disorder (MDD, (Kan et al., 2004; Koch et al., 2018; Liu et al., 2012; Naranjo et al., 2011; Schlipf et al., 2013), and attention deficit hyperactivity disorder (ADHD, (Bisch et al., 2016; Grabemann et al., 2013; Kis et al., 2017).

Concerning the neural basis of prosody processing in healthy participants, neuroimaging studies revealed robust evidence for a neural network showing enhanced reactivity to emotional prosody in the middle part of the right superior/middle temporal gyrus (STG/MTG, (Beaucousin et al., 2006; Dietrich et al., 2008; Ethofer et al., 2006b; Ethofer et al., 2012; Ethofer et al., 2009a; Ethofer et al., 2009b; Ethofer et al., 2007; Grandjean et al., 2005; Schirmer and Kotz, 2006; Wiethoff et al., 2009) as well as the amygdala (Liebenthal et al., 2016; Wiethoff et al., 2009). So far, only a few studies examined differences in neural activation between healthy individuals and psychiatric patient populations during processing of emotional prosody. Mitchell et al. (2004) previously described a diminished neural activity within the STG, inferior frontal gyrus (IFG), and the amygdala in patients with BD during perception of emotional prosody compared to healthy controls (HC). For alexithymia, a reduced neural response to emotional prosody within the right STG and the bilateral amygdala was shown (Goerlich-Dobre et al., 2013). In a recent study, we demonstrated an increased neural activation of the amygdala during prosody processing in patients with MDD as compared to HC, while no differences between groups were found for the STG/MTG (Koch et al., 2018). Although these studies suggest some variation regarding regional changes in activation, STG and amygdala emerge as most frequently involved brain areas across different psychiatric disorders.

One of the most promising genetic risk factors for affective psychiatric disorders is *CACNA1C* (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Ferreira et al., 2008; Ripke et al., 2013; Ripke et al., 2011; Sklar et al., 2011; Sklar et al., 2008). *CACNA1C*

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encodes the alpha 1C subunit of the L-type voltage-gated calcium channel and is primarily expressed in the cardiovascular system but also the brain (Striessnig et al., 2006). The single nucleotide polymorphism (SNP) rs1006737 within *CACNA1C* was one of the first genome-wide significant findings emerging from a GWAS study in psychiatry (Ferreira et al., 2008; Sklar et al., 2008): While it was initially found to be associated with BP, further studies confirmed a role of this SNP also in several other psychiatric disorders including SCZ and MDD (Green et al., 2010; Liu et al., 2011; Rao et al., 2016; Ripke et al., 2013; Ruderfer et al., 2014).

Previous studies investigating the potential function of *CACNA1C* in the etiology of psychiatric disorders have found a link between the rs1006737 risk variant and processing of facial emotions: *CACNA1C* risk allele carriers show slower response times (Nieratschker et al., 2015) and exhibit altered activation of the amygdala (Bigos et al., 2010; Jogia et al., 2011; Tesli et al., 2013) as well as altered connectivity of the amygdala with prefrontal structures (Dima et al., 2013; Wang et al., 2011) during identification of facially expressed emotions. Importantly, the observed physiological changes of amygdala activation and connectivity in *CACNA1C* risk allele carriers were found similarly in HC, psychiatric patients, and their first degree relatives (Jogia et al., 2011; Tesli et al., 2013). Even though the rs1006737 polymorphism is intronic and does not encode an amino acid substitution, it was found to be functionally relevant, presumably affecting CACNA1C expression through proxy or linkage SNP variants (Bigos et al., 2010). So far, no study has been carried out investigating the effect of *CACNA1C* rs1006737 on processing of emotional prosody on a behavioral or neural level.

Affective psychiatric disorders are frequently associated with white matter abnormalities (Sexton et al., 2009). A limited number of studies addressed the impact of *CACNA1C* on the microstructure of the brain. They demonstrated a reduction of fractional anisotropy (FA) in *CACNA1C* rs1006737 risk allele carriers in several brain regions, in HC (Dietsche et al., 2014; Woon et al., 2017), BD patients (Woon et al., 2017) and SCZ patients (Mallas et al., 2017). However, none of these studies specifically investigated areas implicated in emotion processing and all were restricted to changes in FA.

In the current study, we combine functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to examine the effect of the *CACNA1C* risk allele rs1006737 on structure and function of critical areas (i.e. STG/MTG and amygdala) for processing of emotional prosody in a healthy population. Our combined approach allowed us to investigate possible influences of this risk allele manifesting in changes of behavior and corresponding functional activation during evaluation of emotionally relevant stimuli as well as the underlying microstructure characterized by altered diffusion parameters, with FA and mean diffusivity (MD) as main diffusion parameters. Additionally, we also explored axial diffusivity (AD) and radial diffusivity (RD). Based on previous structural and functional studies regarding changes associated with the *CACNA1C* risk allele rs1006737 (for a review, see (Ou et al., 2015)), as well as own examinations on processing of prosody in depressed patients (Koch et al., 2018), we hypothesize that such alterations would affect the amygdala, but not the temporal voice areas. Examining genetic risk variants in healthy individuals represents a promising strategy that can pave the way for a better understanding of the mechanisms underlying altered perception and neural processing of emotions in psychiatric patient populations without being compromised by typical confounding variables, such as disease duration, medication or epistasis with other risk alleles (for a similar approach see (Wessa et al., 2010)).

2. Materials and methods

2.1. Participants

51 healthy, right handed German native speakers (27 women, mean age ± SD 29.6 ± 9.6 years) were included in the study. Righthandedness was assessed with the Edinburgh Inventory (Oldfield, 1971). Participants were recruited via public announcements and screened beforehand for any current and/or history of neurological and/or psychopathological impairments by trained psychologists, using the SCID I and SCID II interviews (First et al., 1997; First et al., 1995). The general exclusion criteria for MRI examinations (metal implants, non-removable metal jewelry, tattoos with possibly metal containing colorants, and claustrophobia) were applied. Verbal intelligence and executive functioning were assessed using the Mehrfachwortschatztest, (MWT-B, Multiple-Choice Vocabulary Intelligence Test, (Lehrl, 1977) and Wisconsin Card Sorting Test (WCST, (Heaton & Staff, 1993), respectively. The study conformed to the code of Ethics of the World Medical Association (Declaration of Helsinki) and the study protocol was approved by the local ethics committee (Ethics committee of the medical faculty of the University of Tuebingen, Eberhard-Karls-University Tuebingen). All participants gave written informed consent to the study.

2.2. Genotyping

Genomic DNA was extracted from ethylenediaminetetraacetic acid (EDTA) anti-coagulated venous blood using the QIAamp DNA Blood Maxi-Kit (Qiagen; Hilden; Germany). *CACNA1C* rs1006737 was genotyped on a StepOne system using TaqMan® SNP Genotyping Assay C__2584015_10 (Thermo Fisher Scientific, Waltham, U.S.). Accuracy was assessed by duplicating 20% of the original sample, and reproducibility was 100%. The genotype frequencies did not deviate from Hardy–Weinberg equilibrium ($p > .05$).

2.3. Stimulus material and experimental design

Voice recordings of single German words, adjectives with a positive, neutral and negative connotation, were used as stimuli. The recorded adjectives were selected from a pool of 500 words based on valence ratings obtained from 45 healthy German native speakers (Herbert et al., 2006). The stimuli were spoken by three female and three male professional actors with happy, neutral, or angry intonation (3 prosodic categories × 27 words = 81 stimuli) and subsequently normalized to the same peak volume. The mean durations ± standard deviation were 709 ± 237 ms for happy stimuli, 699 ± 223 ms for neutral stimuli, and 803 ± 350 ms for angry stimuli with no significant differences between categories (all $p > .05$). Independent ratings for classification of the expressed emotional valence were obtained, validated and replicated in former studies (for a detailed description, see (Ethofer et al., 2006a; Ethofer et al., 2006b; Schlipf et al., 2013). The experiment consisted of two blocks, in which participants were asked to judge the emotional valence of the prosody of presented words on a visually presented 5-point Likert scale (Bradley and Lang, 1994) ranging from −− (strongly negative), − (slightly negative), 0 (neutral), + (slightly positive), to ++ (strongly positive). To minimize biases due to the specific finger used to respond, the orientation of the scale was flipped for half of the participants. In addition, a voice localizer was employed to determine voice-sensitive areas, consisting of a passive-listening block design experiment with 32 stimulations (16 human voices (HV), 8 animal sounds (AS) and 8 environmental sounds (ES) as well as 16 silent epochs, 8 s each, (Belin et al., 2000). Stimuli were presented via MRI-compatible headphones. Stimulus presentation and recording of behavioral responses was carried out using the software Presentation (Neurobehavioral Systems, www.neurobs.com). The acquisition of behavioral data was achieved using an MRI-compatible response system for five fingers (Celeritas Fiber Optic Button Response System, Psychology Software Tools). Reaction times were obtained and we instructed the participants to respond quickly, but emphasized that correct responses regarding their individual perception of the stimuli are more important than speed.

2.4. Neuroimaging data acquisition

MRI data were acquired with a 3T scanner (PRISMA, Siemens, Erlangen, Germany) using a 20 channel head coil. High resolution structural T1-weighted images (TR = 2.3 s, TE = 4.16 ms, TI = 0.9 s, voxel size: $1 \times 1 \times 1\,mm^3$) and functional images (72 slices, slice thickness 2 mm + 1 mm gap, TR = 1.5 s, TE = 34 ms, voxel size: $2 \times 2 \times 2\,mm^3$, multi-band acceleration factor 3) were collected. Time series consisted of 301 and 308 images for the two sessions of the main experiment (prosody judgment) and 273 functional images for the voice localizer (72 slices, slice thickness 2 mm + 1 gap, TR = 1.5 s, TE = 34 ms, voxel size, $2 \times 2 \times 2\,mm^3$, multi-band acceleration factor 3). For image distortion correction, a field map (36 slices, slice thickness 3 mm + 1 gap, TR = 0.4 s, TE(1) = 5.19 ms, TE(2) = 7.65 ms, voxel size: $3 \times 3 \times 3\,mm^3$) was obtained. Diffusion weighted images were acquired (TR = 6 s, TE = 52 ms, bandwidth: 1930 Hz/voxel, flip angle = 90°, 64 axial slices, 2 acquisitions) with a voxel size of $2 \times 2 \times 2\,mm^3$ along 30 independent directions using a b-value of $1000\,s/mm^2$. Additionally, an image with a b-value of $0\,s/mm^2$ was acquired for coregistration.

2.5. fMRI processing

Functional images were processed and analyzed using statistical parametric mapping software (SPM12, Wellcome Trust Center for Neuroimaging, UCL, London, UK). Preprocessing comprised slice time correction, realignment, unwarping to correct for field distortions and to remove residual movement-related variance due to interactions between motion and field distortions (Andersson et al., 2001), normalization to MNI space (Montreal Neurological Institute, resampled voxel size: $2 \times 2 \times 2\,mm^3$) based on the unified segmentation approach integrated in SPM (Ashburner and Friston, 2005) and smoothing with a Gaussian filter (6 mm full width at half maximum).

The first five EPI images of each session were discarded from analysis to exclude measurements preceding T1 equilibrium. Statistical analysis relied on a general linear model (GLM). For the two sessions on prosody judgments, separate regressors were defined for each condition (positive, neutral, and negative prosody) using a stick-function convolved with the hemodynamic response function (HRF). Events were time-locked to the onset of stimulus presentation. For the voice localizer session the three categories of the voice localizer were modeled using a box-car function of 8 s duration convolved with the HRF. To correct for low-frequency components, a high-pass filter with a cutoff frequency of 1/128 Hz was used. Data from the individual first-level GLMs were employed to create contrast images and subsequently submitted to a second-level random effects analysis. For the main experiment, we contrasted emotional (positive and negative) versus neutral prosody. For the voice localizer, responses to HV were contrasted to AS and ES, separately, and a conjunction analysis (Nichols et al., 2005) (HV > AS) ∩ (HV > ES) was carried out to confirm that enhanced responses to emotional versus neutral prosody are situated within the voice-sensitive cortex.

Assignment of anatomical structures to activation clusters relied on the automatic anatomical labeling tool integrated in SPM (Tzourio-Mazoyer et al., 2002). Cortical and subcortical fMRI activations are reported using a height threshold of $p < .05$ (FWE corrected) and an additional extent threshold of $k \geq 8$ voxels of the main experiment, and a height threshold of $p < .01$ (FWE corrected) and an additional extent threshold of $k \geq 60$ voxels for the voice localizer. Voxels within the gray matter of superior and middle temporal gyrus (STG/MTG, as defined by BCI-DNI brain atlas (http://brainsuite.org/atlases/) showing significant effects in the group analysis were defined as voice-sensitive area. Beta estimates of the amygdala and the voice-sensitive area were extracted and submitted to a 3 × 2 repeated-measures ANOVA with emotion (happy, neutral, angry) as within- and group as between-subjects factor (*CACNA1C* risk allele carriers (AA/AG) vs. non carriers (GG)).

2.6. DTI processing

T1-weighted images were processed using BrainSuite's cortical surface extraction pipeline (http://brainsuite.org/processing/surfaceextraction/v16a), producing surface models of the cerebral cortex from T1 MRI (Shattuck and Leahy, 2002). Image analysis included skull and scalp removal, nonuniformity correction, tissue classification, registration-based identification of the cerebrum, topology correction, and surface generation to produce triangular surface mesh models of the inner and outer boundaries of the cerebral cortex. Next, the surfaces for each participant were registered to a reference atlas surface using BrainSuite's surface/volume registration software (SVReg; http://brainsuite.org/processing/svreg/v16a, (Joshi et al., 2012b; Joshi et al., 2004, 2007) which represents a refined cortical pattern matching procedure that enables cortical surface mapping via alignments between surface features. SVReg finds a one-to-one map between these surfaces via an intermediate flat map (Joshi et al., 2004). Geodesic curvature flow was used to improve registration of the sulcul features (Joshi et al., 2012a) resulting in a spatial alignment of the white/gray matter cortical surfaces across subjects.

Diffusion-weighted images where processed with the BrainSuite Diffusion Pipeline (BDP; http://brainsuite.org/processing/diffusion/) including registration based distortion correction using a constrained non-rigid registration. The bias field corrected anatomical image generated by BrainSuite was used as a registration template to constrain the registration using spatial regularization and physics-based characteristics of distortion in EPI sequences (Bhushan et al., 2015). BDP was used to fit tensor models to the diffusion MRI data from which diffusion measures (i.e. MD, **AD, RD** and FA) were computed. Output images from SVReg were then applied to the BDP output images (MD, **AD, RD** and FA) to generate diffusivity values within each labeled region of interest (ROI) comprising the left and right amygdala as defined by the BCI-DNI brain atlas and the left and right voice-sensitive areas (STG/MTG) as defined by the fMRI voice localizer.

2.7. Statistical analysis

Statistical analyses were carried out using SPSS (SPSS, 2012). Demographic differences between genotype groups (*CACNA1C* risk allele carriers (AA/AG) vs. non carriers (GG)) were assessed using two-sample *t*-tests assuming unequal variances across groups. Behavioral responses and reaction times were analyzed using two-sample *t*-tests assuming unequal variances across groups. Mean beta values generated by the individual first-level GLMs of fMRI data within the ROIs (STG/MTG and amygdala) were submitted to a two-factorial ANOVA for repeated measures with emotion (positive, neutral, negative) as within- and group (*CACNA1C* risk allele carriers versus non-risk carriers) as between-subjects factors to assess main effects of group as well as interactions between group and emotion. Two-sample t-tests assuming unequal variances across groups were carried out to compare group differences for each emotion category and cluster separately. The effect of rs1006737 on the diffusivity values (MD, **AD, RD** and FA) was evaluated by multivariate analyses of variance (MANOVA) with age and sex as covariates of no interest. All resulting *P* values were corrected for heterogeneous correlations (Geisser and Greenhouse, 1958) and considered significant for $p < .05$.

3. Results

3.1. Genotypes

The studied group contained 26 carriers of the *CACNA1C* rs1006737 risk allele (AA/AG: 10 women, mean age ± SD 29.0 ± 8.7 years) and 25 individuals homozygous for the non-risk genotype (GG: 17 women,

Table 1
Demographics of the study sample genotyped for *CACNA1C* rs1006737.

	AA/AG (n = 26)	GG (n = 25)	p-Value
Sex ratio (female/male)	10/15	17/9	*ns*
Age (M ± SD, years)	29.0 ± 8.7	30.2 ± 10.2	*ns*
Education (M ± SD, years)	16.9 ± 3.1	15.9 ± 3.0	*ns*
MWT-B (M ± SD, IQ)	107 ± 14.8	109 ± 14.4	*ns*
WCST (M ± SD, score)	6.09 ± 2.4	6.20 ± 1.9	*ns*

M, mean; SD, standard deviation; AA/AG: risk allele carriers of *CACNA1C* rs1006737; GG: non-risk allele carriers of *CACNA1C* rs1006737; ns, not significant.

mean age ± SD 30.2 ± 10.2 years). No significant differences in sex, age, education, verbal intelligence and executive functioning were found between genotype groups (AA/AG vs. GG individuals). All sociodemographic data are presented in Table 1.

3.2. Behavioral data

Valence judgments and reaction times obtained during the main fMRI experiment are shown in Fig. 1. No significant differences between genotype groups were found for judgment of positive (t (49) = 1.02, p = .311), neutral (t(49) = −1.67, p = .102) or angry prosody (t(49) = 0.51, p = .960). Similarly, no significant differences between groups were found in reaction times to positive (t(49) = 0.82, p = .415), neutral (t(49) = 0.46, p = .648) or angry prosody stimuli (t (49) = 0.67, p = .506).

3.3. fMRI data

As predicted, the whole-brain analysis yielded stronger activations in bilateral STG/MTG and amygdala for trials with emotional as compared to neutral prosody (see Table 2 and activations in red/yellow in Fig. 2, upper panel). The activations in STG/MTG were situated within the voice-sensitive areas (see activations in blue/light blue in Fig. 2, upper panel). A 3 × 2 repeated measures ANOVA with emotion as within-and genotype as between-subject factor main effect for emotion was found in the left amygdala [F (2, 48) = 36.87, p < .001, partial η^2 = 0.61] and the right amygdala [F (2, 48) = 30.33, p < .001, partial η^2 = 0.56], as well as the left STG/MTG [F (2, 48) = 70.31, p < .001, partial η^2 = 0.75] and the right STG/MTG [F (2, 48) = 70.62, p < .001, partial η^2 = 0.75]. No main effects of genotype group nor an interaction between genotype and emotion were found in the amygdala and/or voice areas (all F < 1.9, all p > .171).

3.4. DTI data

MANOVAs were conducted to assess microstructural differences in two ROIs (amygdala, voice areas) between genotype groups (AA/AG vs. GG individuals). Significantly lower MD was found in risk allele carriers compared to non-risk allele carriers in the right amygdala [F (1, 47) = 6.10, p < .017, partial η^2 = 0.115] and the left amygdala [F (1, 47) = 4.31, p < .043, partial η^2 = 0.084] (Fig. 3, upper panel; Table 3). No significant differences between genotype groups were found in FA in the left or right amygdala (all p > .05; Fig. 3, upper panel; Table 3). No significant microstructural differences were found in MD or FA between genotype groups in the left or right voice areas (all p > .05; Fig. 3, lower panel; Table 3). The additional analyses (see Supplementary Material) regarding AD and RD revealed significantly lower values for AD in the right amygdala (p = .012) of risk allele carries. In the left amygdala, this effect scarcely failed to reach significance (p = .055).

Table 2
Significantly activated clusters in the univariate analysis emotional vs neutral prosody.

Anatomical definition	MNI coordinates	Z score	Cluster size
Left superior/middle temporal gyrus	[−48–22 6]	6.39	969
Right superior/middle temporal gyrus	[58–12 -2]	6.23	748
Left Amygdala	[−20–8 -12]	6.05	37
Left frontal Inferior opercularis	[−52 10 14]	5.71	45
Left Insula	[−40–8 -14]	5.57	18
Left posterior orbitofrontal cortex	[−36 26–16]	5.43	43
Left precentral gyrus	[−32–28 58]	5.32	49
Right superior/middle temporal pole	[38 20–30]	5.32	10
Right Amygdala	[20–6 -14]	5.18	9
Left middle temporal gyrus	[−56 2–16]	5.06	11
Left superior/medial frontal gyrus	[−2 44 36]	5.05	9
Right superior temporal gyrus	[54–4 -14]	5.04	11
Right calcarine fissure	[18–62 4]	4.97	10

Order of clusters is by cluster size. Locations of peaks are labeled with the AAL atlas (Tzourio-Mazoyer et al., 2002).

4. Discussion

This is the first study to investigate the influence of *CACNA1C* rs1006737 on structure and function of key areas for perception of emotional prosody using an imaging genetics approach in healthy individuals. In line with previous studies, emotional prosody enhanced activation in the STG/MTG and the amygdala (Ethofer et al., 2006b; Ethofer et al., 2009a; Ethofer et al., 2009b; Ethofer et al., 2007; Frühholz et al., 2011; Grandjean et al., 2005; Liebenthal et al., 2016; Wiethoff et al., 2009; Wiethoff et al., 2008). Our study specifically targeted these areas in a combined fMRI/DTI study to clarify to which extent *CACNA1C* impacts their activation and brain microstructure.

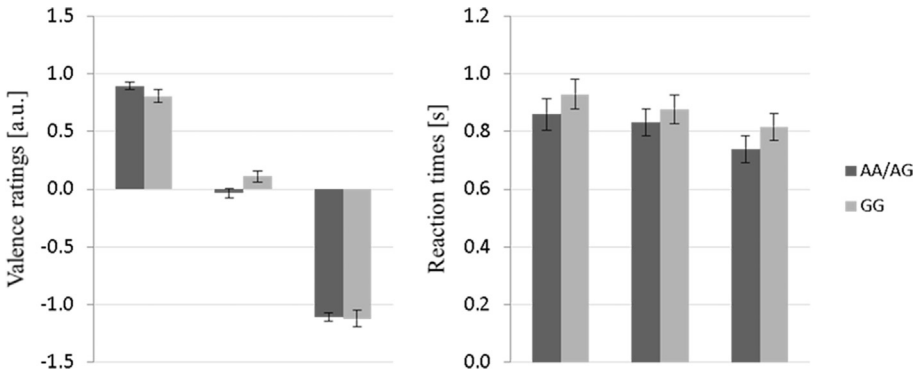

Fig. 1. Valence ratings (mean values ± SE) of emotional prosody and reaction times obtained in risk allele carriers (AA/AG, dark gray) and non carriers (GG, light gray) for positive (left bars), neutral (center bars), and negative (right bars) prosody; a.u., arbitrary unit; s, seconds.

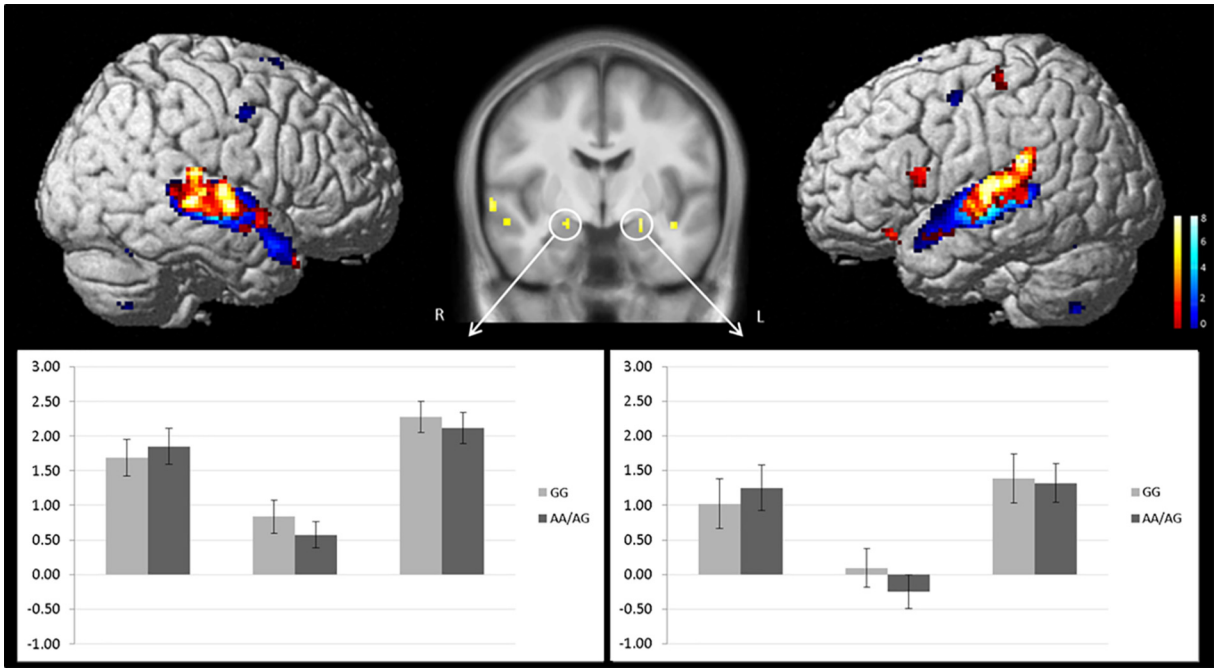

Fig. 2. Neural activation cluster in the right (upper panel, left) and left (upper panel, right) hemisphere during emotional > neutral prosody (red-yellow) and voice-sensitive areas as defined by the fMRI localizer experiment (blue-light blue) and amygdala activation clusters (upper panel, center) (threshold of activation level $p < .05$, FWE corrected) with beta estimates (mean ± SE) in the right (lower panel, left) and left (lower panel, right) amygdala in AA/AG risk allele carriers of *CACNA1C* rs1006737 (dark gray) and GG non carriers (light gray) during positive (left bars), neutral (center bars), and negative (right bars) emotional information.

4.1. Behavior

The SNP rs1006737, located in intron 3 of the *CACNA1C* gene has been identified as risk factor for psychiatric disorders in genome-wide association studies (Ferreira et al., 2008; Green et al., 2009; Nyegaard et al., 2010; Rao et al., 2016; Sklar et al., 2008) as well as several follow-up studies (for a review, see (Berger and Bartsch, 2014)). As rs1006737 is located in an intron it is not influencing *CACNA1C* function directly (i.e. by amino acid substitution in the encoded protein). Nevertheless, rs1006737 is still potentially functionally relevant, as a proxy variant for this SNP (rs2159100) was found to be associated with increased gene expression in the brain (Bigos et al., 2010). Moreover, it has been demonstrated that even healthy subjects carrying the rs1006737 risk allele exhibit impaired cognitive resources including altering and orienting (Thimm et al., 2011) as well as lexical verbal fluency (Krug et al., 2010). In our study, however, no significant differences in valence judgment of prosodic emotions were found. This lack of behavioral effects during processing of emotionally relevant stimuli concurs with previous results obtained during reward processing (Wessa et al., 2010) or rating of affective pictures (Pasparakis et al., 2015). Similarly, a study examining facial emotions based on the reading-the-mind-in-the-eyes-task also failed to show significant differences in emotional judgments, but yielded prolonged reaction times in carriers of the risk allele (Nieratschker et al., 2015). In our study, no differences in reaction times were found which could be due to the fact that we did not instruct the study participants to respond as quickly as possible. In summary, our behavioral results are in agreement with the previous findings observed across several different types of emotionally relevant stimuli suggesting that healthy individuals with the risk allele of rs1006737 are not considerably burdened on a behavioral level by altered perception of emotional stimuli even if significant changes in cerebral processing (e.g. within the amygdala, (Wessa et al., 2010) or in psychophysiological responses, such as the startle reflex (Pasparakis et al., 2015), are found.

4.2. Structure and function of prosody processing regions

A recent review (Ou et al., 2015) summarized the observed alterations in brain structure and functional activation associated with the *CACNA1C* risk allele of SNP rs1006737. The evidence gathered across several studies in different labs suggests a dose-dependent effect resulting in higher gray matter density in the amygdala and frontal areas of individuals with the risk allele occurring similarly in patients with psychiatric disorders and healthy controls. Our structural findings including reduced MD values in risk allele carriers and thus a higher membrane density (for a review on the interpretation of diffusion scalars see (Alexander et al., 2011)) are fully compatible with these previous findings. In line with our a priori hypothesis, this effect was restricted to the amygdala and not observed in the STG/MTG.

In addition, we also found lower values for AD in the amygdala of risk allele carriers. As AD has been repeatedly reported to increase with brain maturation (Ashtari et al., 2007; Bava et al., 2010; Gao et al., 2009) this finding might point to less mature neural structures within the amygdala of individuals with the risk allele of SNP rs1006737. However, it has been noted that assessment of diffusion scalars (other than MD) are particularly challenging in areas with crossing fibers (Wheeler-Kingshott and Cercignani, 2009). As the amygdalae do not represent a homogenous white matter structure with one predominant fiber orientation, but a gray matter complex consisting of several different subnuclei with intensive connectivity as well as various inputs from and outputs to other neural structures (Janak and Tye, 2015), this result requires careful interpretation.

Regarding functional activation in emotion processing paradigms the effect of SNP rs1006737 on amygdalar activity of healthy subjects is less clear. A previous study using emotional (angry and fearful) faces reported a trend towards increased activation in the right amygdala of risk allele carriers which failed to reach significance (Bigos et al., 2010). A second study using the same paradigm on emotional face processing revealed significantly increased activation within the left amygdala in risk allele carriers (Tesli et al., 2013). This effect was shown for a sample of bipolar patients as well as a mixed sample including healthy

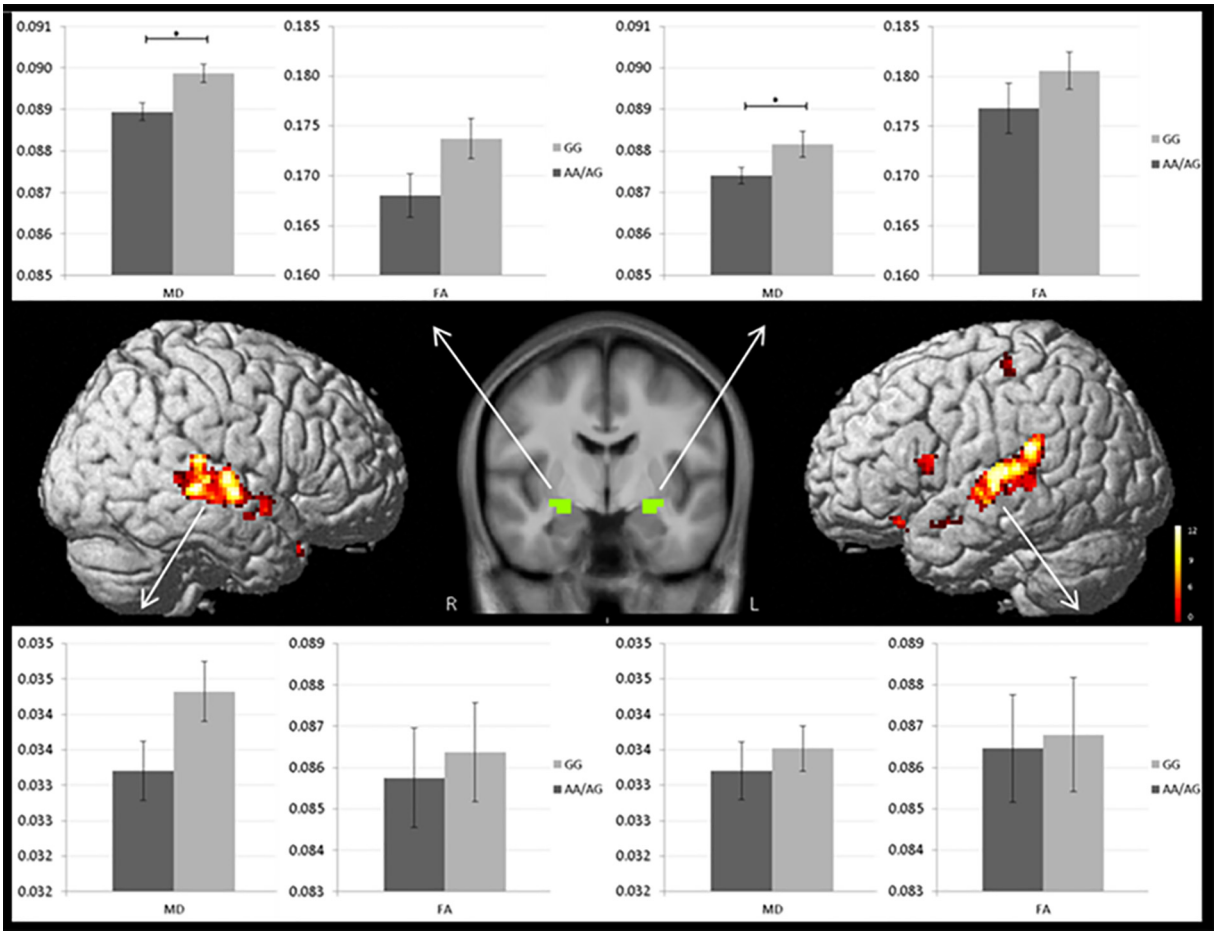

Fig. 3. Voice-sensitive areas in the right (middle panel, left) and left (middle panel, right) hemisphere as defined by the fMRI localizer experiment (threshold of activation level $p < .01$, FWE corrected). Right and left amygdala (middle panel, center) as defined by AAL (Tzourio-Mazoyer et al., 2002). Diffusivity values (mean ± SE) of AA/AG risk allele carriers of *CACNA1C* rs1006737 (dark gray) and GG non carriers of *CACNA1C* rs1006737 (light gray) in the right (upper panel, left) and left (upper panel, right) amygdala and the right (lower panel, left) and left (lower panel, right) voice area. Displayed are mean diffusivity (MD) (mean units: 10^{-3} s/mm^2) and fractional anisotropy (FA). Significant group differences are marked by asterisks (*$p < .05$).

Table 3
MANOVA effects of *CACNA1C* rs1006737 on MD and FA.

Region		AA/AG (n = 26)		GG (n = 25)		
	DP	*M*	*SD*	*M*	*SD*	*P*
R Amygdala	MD	0.889	0.015	0.899	0.016	***0.017***
	FA	0.168	0.0156	0.174	0.014	*0.162*
L Amygdala	MD	0.869	0.015	0.877	0.023	***0.043***
	FA	0.177	0.018	0.181	0.013	*0.390*
R Voice Area	MD	0.332	0.030	0.343	0.030	*0.488*
	FA	0.085	0.009	0.086	0.009	*0.772*
L Voice Area	MD	0.332	0.029	0.335	0.023	*0.857*
	FA	0.086	0.009	0.086	0.010	*0.750*

M, mean; SD, standard deviation; AA/AG, risk allele carriers of *CACNA1C* rs1006737; GG, non-risk allele carriers of *CACNA1C* rs1006737; R, Right; L, Left; DP, Diffusivity Parameter; MD, mean diffusivity (MD mean units: 10^{-3} s/mm^2); FA, fractional anisotropy. Significant post-hoc corrected results are in **BOLD ($p < .05$)**.

controls and patients with schizophrenia or bipolar disorder, but the authors did not report results which were restricted to the healthy risk allele carriers making it impossible to differentiate between effects attributable to the risk allele versus psychiatric disorders. So far, no data are available examining the effects of the *CACNA1C* risk allele of SNP rs1006737 on processing of vocal emotions. In our study, direct comparison of neural activations between groups revealed no significant differences between genotype groups within the STG/MTG or the amygdala. Thus, the combined structural and functional results of our study indicate that the risk allele is associated with alterations of microstructure rather than functional activation of the amygdala as potential early neurobiological substrate for the development of affective disorders. Changes in functional activation and corresponding behavior as observed in depressed patients (Koch et al., 2018) might occur only when the affective disorders already manifested itself as e.g. demonstrated for risk allele carriers with bipolar disorder (Tesli et al., 2013).

5. Conclusion and outlook

This is the first study investigating the role of *CACNA1C* rs1006737 on prosody perception and processing on a behavioral, functional and structural level in a healthy population. Our findings reveal an effect of *CACNA1C* genotype on amygdalar microstructure with reduced MD in risk allele carriers indicating higher membrane density and thus cellularity within this region. These microstructural alterations were not associated with changes in behavior or functional activation. The results of our study could constitute a first step for a better understanding of the neurobiological substrates underlying the development of affective disorders in individuals with the risk variant of *CACNA1C* rs1006737. However, this study was carried out with healthy participants only and a rather small sample size requiring careful interpretation. Future studies based on a longitudinal approach are needed to address the hypothesis brought forward here that microstructural

changes represent an early brain marker, which is accompanied by altered functional activation at later stages in the course of affective disorders.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101774.

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